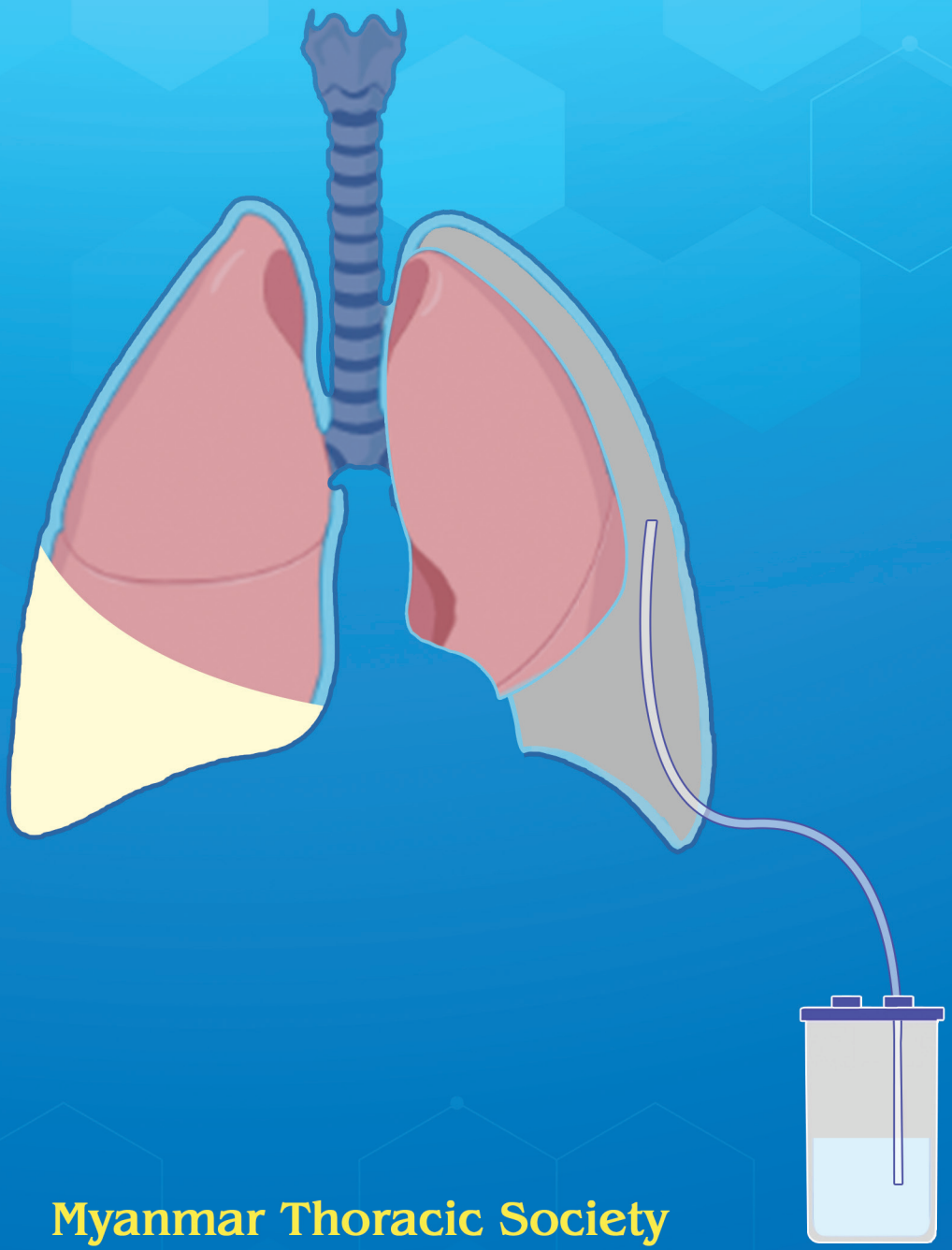
Clinical Practice Guidelines for Management of Pleural Diseases



Myanmar Thoracic Society

2024

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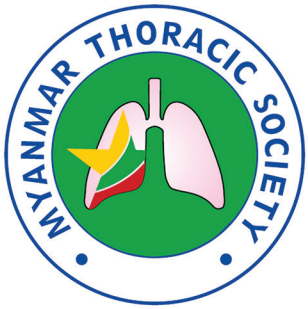

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Acknowledgement

On behalf of Myanmar Thoracic Society, we would like to express gratifying words to those who gave a helping hand in accomplishing this guideline on pleural diseases.

First and foremost, we extend our heartfelt thanks to Prof. Tin Maung Cho, for his unwavering guidance, invaluable insight and relentless efforts throughout the entire process. His expertise and commitment have tremendously enriched the quality of this work.

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In conclusion, this guideline on pleural diseases stands as a proof to the collective efforts of the aforementioned individuals and members of Myanmar Thoracic Society. Their contributions have left an indelible mark on this work, and for that, we are truly grateful.

Guideline Development Group
Myanmar Thoracic Society

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Abbreviations

ADA	adenosine deaminase
AIDS	acquired immune deficiency syndrome
ANA	antinuclear antibody
APF	alveolar-pleural fistula
ART	antiretroviral therapy
ATS	American Thoracic Society
AUC	area under curve
BMI	body mass index
BPF	bronchopleural fistula
BTS	British Thoracic Society
CAP	community-acquired pneumonia
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
CPPE	complicated parapneumonic effusion
CT	computed tomography
DNase	deoxyribonuclease
ELCs	emphysema-like changes
ESRD	end-stage renal disease
FDC	fixed dose combination
FRC	functional residual capacity
HAP	hospital-acquired pneumonia
HH	hepatic hydrothorax
HIV	human immunodeficiency virus
HR	isoniazid and rifampicin
HREZ	isoniazid, rifampicin, ethambutol, pyrazinamide
IPC	indwelling pleural catheter
IGRA	Interferon Gamma Release Assay
MDR	multi-drug resistance
MGIT	Mycobacteria Growth Indicator Tube
MPE	malignant pleural effusion
MPM	malignant pleural mesothelioma

MRSA	methicillin-resistant Staphylococcus aureus
Mtb	Mycobacteria tuberculosis
MTB/RIF	Mycobacterium tuberculosis and rifampicin resistance
NAAT	nucleic acid amplification testing
NPV	negative predictive value
NT proBNP	N terminal pro-B-type natriuretic peptide
PAL	persistent air leak
PCR	polymerase chain reaction
PET-CT	positron emission tomography – computerized tomography
PMN	polymorphonuclear leukocytes
PPE	parapneumonic effusion
PPV	positive predictive value
PSP	primary spontaneous pneumothorax
qSOFA	quick sepsis-related organ failure assessment
RAPID	Renal (urea), Age, fluid Purulence, Infection source, Dietary (albumin) score
RCT	randomized controlled trial
RNA	ribonucleic acid
γINF	interferon gamma
RPT	residual pleural thickening
SACT	systemic anti-cancer therapy
SP	spontaneous pneumothorax
SPPE	simple parapneumonic effusion
SSP	secondary spontaneous pneumothorax
TIMP1	tissue inhibitor of metalloproteinases 1
TIPS	transjugular intrahepatic portosystemic shunts
TNF α	tumor necrosis factor alpha
t-PA	tissue plasminogen activator
TPE	tuberculous pleural effusion
TUS	thoracic ultrasound
VATS	video assisted thoracoscopic surgery
VEGF	vascular endothelial growth factor

Executive summary

Clinical pleural problems are frequently encountered in conditions requiring decisive management. Although principles of management are not new and well known to most practitioners, the strategy of treatment differs between practitioners and may affect the outcomes which should be the best obtainable from the patient's point of view. As experience and research accumulates, evidence-based information is emerging. This guideline tries to provide scientific practice and advice, mentioning some theoretical basis where necessary. Points of importance are highlighted at the end of each section. A few algorithms (flow charts) are provided in some sections, but they are just general guides to diagnosis and treatment showing necessary steps. Individualized treatment may not require strict following of the sequences. It starts with pertinent clinical physiology of pleural cavities and then proceeds to subsequent sections to provide a smooth flow of reading for the user.

Applied anatomy and physiology

The constitution of pleura and normal physiological changes of intrapleural pressures are described. The formation of pleural fluid is explained in details and how consequences of the changes become pathophysiological basis for diseases is hinted.

Pleural effusion

As accumulation of abnormal amounts of fluid is the commonest presentation in pleural diseases, this section contributes a major part to this guideline. Increase in hydrostatic pressure, decrease in oncotic pressure, changes in permeability and adverse effects on lymphatic drainage are the basis of the pathophysiology and each contributes variably in different pleural effusions.

General principles of management of pleural effusion are discussed. Importance of clinical evaluation is repeatedly reminded. How to interpret basic investigations with chest X ray, thoracic ultrasound, pleural fluid analysis including cytology and tissue biopsy wherever applicable is described in details. In addition to specific causal treatment, thoracentesis as a form of palliation is emphasized.

Pleural infections

This section deals with three main conditions viz: complicated parapneumonic effusion, empyema and tuberculous pleural effusion.

Clinical awareness for transition of simple parapneumonic effusion to complicated parapneumonic effusion is pivotal to successful management. Appropriate antibiotics and timely intervention for fluid evacuation is emphasized. A caution is here given that ineffective treatment may be associated with significant morbidity and mortality.

Empyema thoracis is the result of delayed or suboptimal management of complicated parapneumonic effusion. While a very early stage of the disease may be tackled with a relatively conservative treatment (repeated aspirations and antibiotics) most of the patients need surgical intervention of some kind for cure/conservation of lung function.

Tuberculous pleural effusion is discussed extensively as it is perhaps the most common pleural effusion at all ages in our community. Pathogenesis is briefly mentioned to give a theoretical basis for diagnostic investigations and treatment. A definitive diagnosis requires demonstration of Mycobacterium tuberculosis bacilli in the biological fluid or tissue. But being unable to demonstrate it in all cases, a confident working diagnosis can be made with other investigations such as histopathological pictures in biopsied tissues. Treatment, once the diagnosis is made, is relatively straight forward using standard anti-TB regimen as in pulmonary tuberculosis. Here again it should be known that delayed and improper treatment (both in composition and duration) may leave a permanent anatomical and functional defect.

Malignant pleural effusion

A common presentation of cancer, in our practice, is pleural effusion termed malignant pleural effusion. It is mostly due to metastasis from a nearby or a distant tumor. Tumors of pleural tissue presenting as an effusion is a rarity. Diagnosis requires cytological proof or histopathological examination. Immunohistochemistry stain can suggest the primary source of malignant pleural effusion in some cases. Treatment is only palliative. The aim is to maintain a reasonable quality and dignity of life until the last day. Treatments to this end comprises of relief of breathlessness (by evacuation of fluid, obliteration of pleural cavity to prevent re-accumulation of fluid) and adequate relief of pain. Treatment of the primary tumor should be considered as appropriate. Management of co-morbidities should never be neglected and participation of the patient and family members in decision making is stressed.

Pneumothorax

This is a frequently encountered clinical problem for every practitioner. It may present as a usual outpatient consultation or as an acute breathlessness or even as a live-threatening state which needs quick recognition and immediate actions.

Types of pneumothoraxes are well explained. Air is a total stranger to pleural cavity and thus an irritant. Obviously, the treatment will be evacuation of air from the pleural cavity. 'When to' and 'how to' (evacuation of air) are discussed in details. A practical concern with pneumothorax is recurrences after the first episode. They are definite indicators for interventional treatment (preventive), especially in patients with high risks (e.g. pilots and divers) and effective means are described.

Malignant pleural mesothelioma

Mesothelioma is a complex group of pathological states beyond the scope of this guideline. However, malignant pleural mesothelioma is briefly touched here as it is a well-known disease of pleura. It is mainly associated with exposure to asbestos many years ago. Treatment is still unsatisfactory although many new targeted therapies have been tried and efforts in this direction is on-going.

Chylothorax

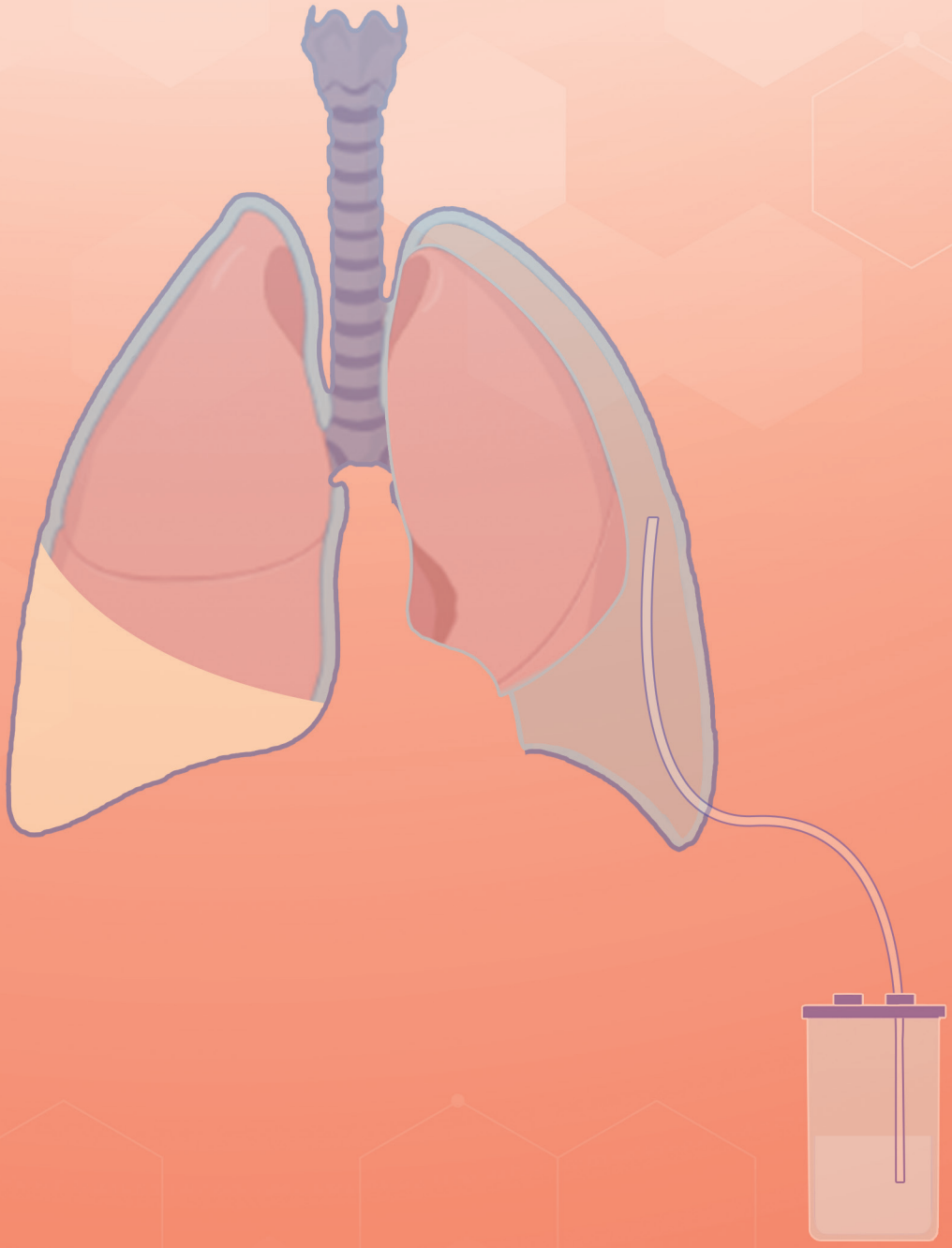
When chyle, fat absorbed from the gastrointestinal tract, enters the pleural cavity it is known as chylothorax and clinically presented as pleural effusion. Its pathogenesis is explained, and diagnosis and treatment are described. A clinical mimicry, pseudo-chylothorax, is also mentioned as a differential diagnosis in workup.

Some common pleural effusions associated with non-pulmonary diseases

Pleural effusion as a presenting/co-existing clinical feature is encountered in many extra-thoracic and systemic diseases. A few common clinical states associated with pleural effusion are discussed. It includes cardiac failure, cirrhosis of liver, and renal insufficiency.

Full descriptions and management of each disease state ensue in the following sections.

1 Pleural Diseases



1. Pleural Diseases

1.1. Introduction

Pleural diseases are common problems, presenting as entities in themselves or as part of a wide-ranging number of other medical and surgical illnesses. It can be associated with significant morbidity and mortality[1]. Pleural effusion and pneumothorax are the most frequently encountered pleural problems, and they have multiple causes. Over the past decade, considerable advances in understanding of pleural biology and related pathophysiology provide a more rational basis for medical and surgical management. The guideline describes diagnosis, investigations and current management of pleural diseases based upon up-to-date evidences.

1.2. Aim

The guideline is aimed to deliver updated knowledge and practice to the clinicians involved in the management of pleural diseases. It provides the clinicians with evidence-based guidance on diagnosis and decision making in clinical management.

1.3. Applied anatomy and physiology of pleura

The pleural cavity is situated between the parietal pleura (outer layer), that is attached to the chest wall and the visceral pleura (inner layer) that covers the lungs. The pleura is composed of mesothelial cells and underlying connective tissue containing blood vessels and lymphatics. The visceral pleura receives its blood supply from the bronchial circulation, while the parietal pleura receives its blood supply from the intercostal arteries. The lymphatic system of the pleura, parietal pleura in particular, is unique. Stomata, cylindrical-like openings with a diameter of 0.5 to 20.0 nm, are formed by discontinuities of the parietal mesothelium and sub-mesothelial interstitial space, and they are the origin of the parietal pleural lymphatic system. However, there are no stomata in the visceral mesothelium. [2]

At functional residual capacity (FRC) the intrapleural pressure is approximately –6 cm H_2O. The negative intrapleural pressure is created by the elastic recoil force of the lung opposed to the tendency of the chest wall to expand. During inspiration, a decrease in pleural pressure is generated with enlargement in the thoracic cage volume caused by the contraction of the diaphragm and external intercostal muscles. This process translates into a negative intrapulmonary pressure and

inspiratory airflow. Conversely, during expiration, a decrease in thoracic volume due to relaxation of the diaphragm and inspiratory muscles result in a slightly higher pleural (although still negative) pressure (-3 to - 5 cm H_2O at FRC). This negative intrapleural pressure maintains the lungs at their inflated state. When this negative intrapleural pressure is eliminated, for example, in the setting of pneumothorax or a large pleural effusion, the lungs may collapse owing to their own elastic recoil [2].

In a normal healthy adult, the pleural cavity has minimal fluid, which acts as a lubricant between the two pleural surfaces. The amount of pleural fluid is around 0.1 ml/kg to 0.3 ml/kg and is constantly exchanged. Pleural fluid originates from the vasculature of parietal pleura surfaces and is absorbed back by lymphatics in the dependent diaphragmatic and mediastinal surfaces of parietal pleura. This fluid is both produced and absorbed primarily on the parietal surface and is dependent on the balance of hydrostatic and oncotic pressure differences in the systemic and pulmonary circulations against pressures in the pleural space (Fig.1). Hydrostatic pressure from the systemic vessels that supply the parietal pleura drives the interstitial fluid into the pleural space and hence has a lower protein content than serum. Lymphatic vessels lying in the parietal pleura are responsible for pleural fluid resorption, and the flow rate of these vessels can increase by a factor of approximately 20 in response to increases in pleural liquid formation [2, 3].

Highlight points

- If the negative intrapleural pressure is abolished (e.g., in setting of pneumothora or a large pleural effusion) the lungs will collapse owing to their own elastic recoil.
- The pleural fluid accumulation depends on the balance of hydrostatic and oncotic pressure between pleural space and two circulations of the chest (systemic and pulmonary circulations).

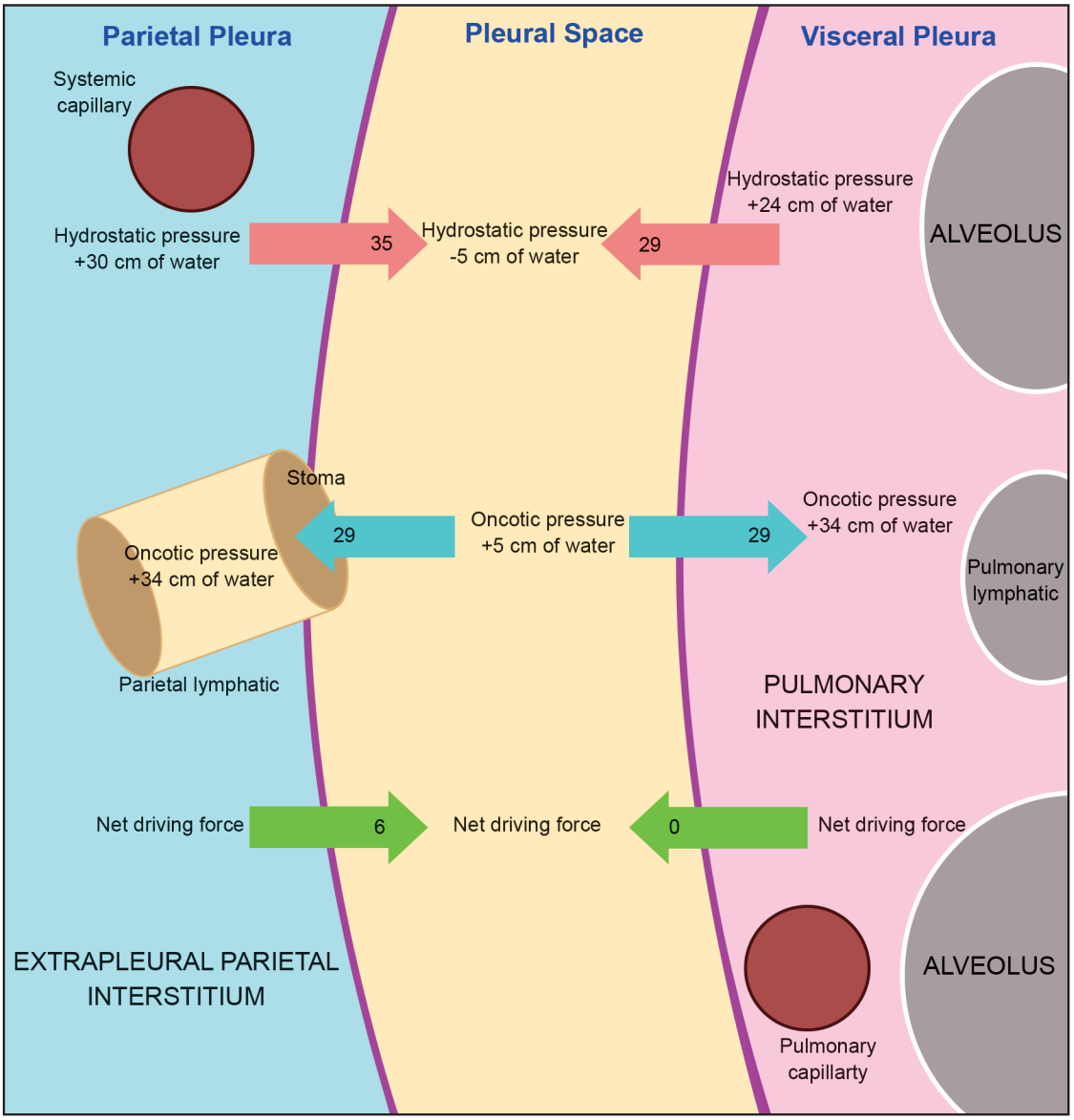
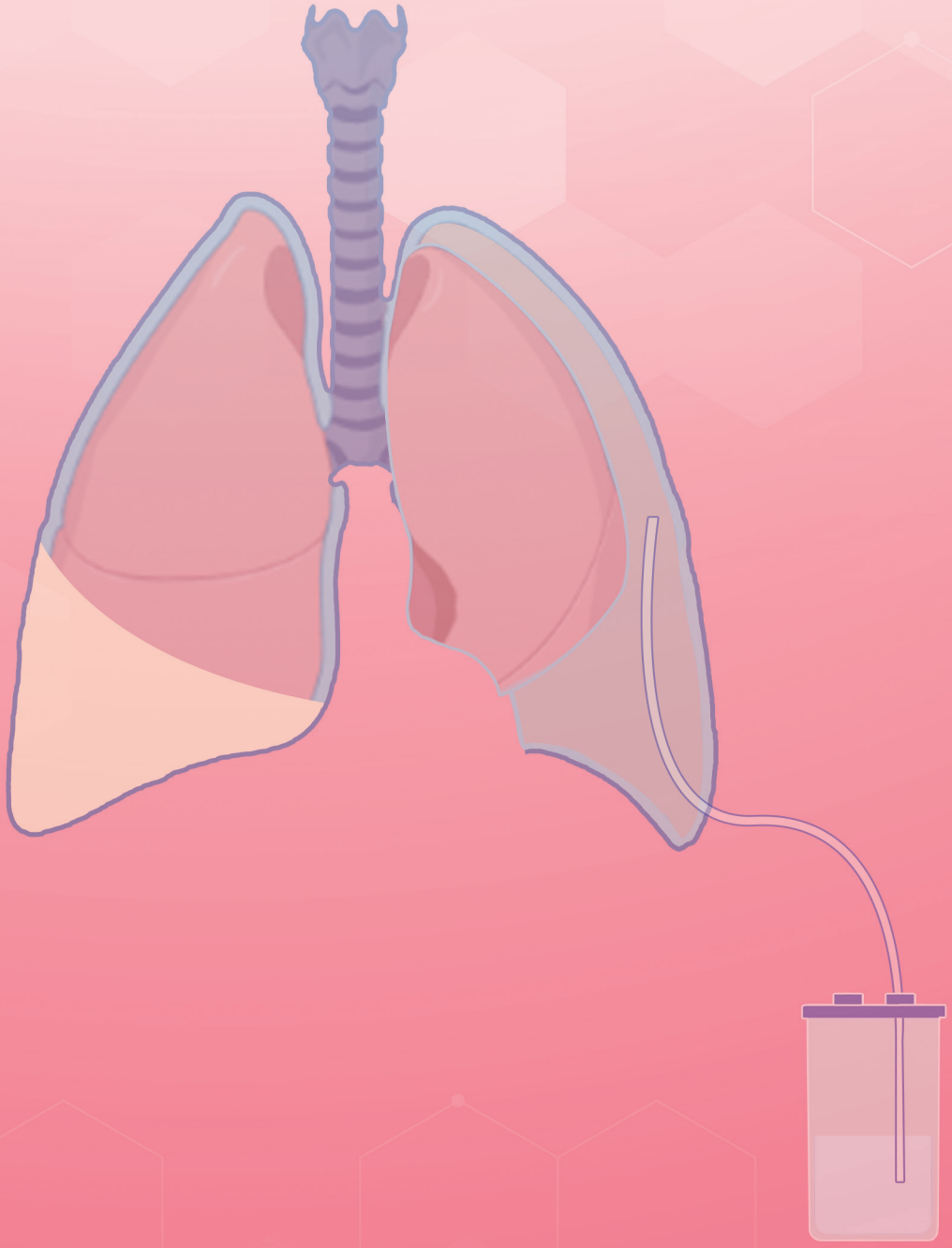


Figure 1. Balance of forces regulating pleural fluid formation [3]

2 Overview of Pleural Effusion



2. Overview of pleural effusion

2.1. Introduction

Pleural effusion is the accumulation of fluid between the parietal and visceral pleura, i.e. in the pleural space. It can occur in diseases of pleura or can be the result of surrounding parenchymal disease such as infection, malignancy, or inflammatory conditions. Pleural effusion is one of the major causes of pulmonary morbidity. A number of systemic medical conditions can also present as pleural effusion without pathological changes in the pleura [3].

Table 1. Causes of pleural effusion

Transudates	Exudates
Common	**Common**
▪ Congestive cardiac failure ▪ Liver cirrhosis ▪ Hypoalbuminemia (e.g., nephrotic syndrome, severe malnutrition)	▪ Malignancy (primary, secondary, mesothelioma) ▪ Pleural infections (parapneumonic effusion, empyema, tuberculosis) ▪ Pulmonary embolism (with infarction)
Less common	**Less common**
▪ Mitral stenosis ▪ Peritoneal dialysis ▪ Chronic hypothyroidism ▪ Constrictive pericarditis	▪ Drugs (nitrofurantoin, dantrolene, bromocriptine. etc.) ▪ Autoimmune pleuritis ▪ Lymphatic disorders (chylothorax, pseudo chylothorax) ▪ Meigs syndrome ▪ Post-coronary artery bypass graft ▪ Benign asbestos related pleural effusion

2.2. Pathophysiology

Within the pleural cavity there is a small amount of fluid (7 - 20 milliliters) (roughly three to four teaspoons) which is continuously filtered and then drained from the pleural space. In contrast, with a pleural effusion this space may expand to contain several liters of fluid, compressing the underlying lungs [3]. The precise pathophysiology of fluid accumulation varies according to underlying cause.

Accumulation of excess fluid can occur if there is increased production or decreased reabsorption, or both, overwhelming the normal homeostatic mechanism. If a pleural effusion is mainly due to increased hydrostatic pressure or decreased oncotic pressure, they are usually transudative.

Increased mesothelial and capillary permeability or impaired lymphatic drainage usually causes exudates [3].

In patients with pleural effusion, the presence of excess fluid within the pleural space can interfere with mechanics of breathing and sometimes causes a medical emergency condition [3]. Detailed pathophysiological changes are described for specific causes in the following sections.

2.3. Clinical evaluation

2.3.1. Symptoms

Breathlessness, chest pain and cough are frequent complaints of patients with pleural effusions, regardless of the underlying cause [4]. Disruption of the shape and function of the diaphragm is the major cause of symptomatology associated with pleural effusion [5].

Breathlessness is the most common symptom in pleural disease and the one that seems most responsive to fluid drainage. It is thought to be largely due to the anatomical and physiological changes caused directly by excess fluid. Moreover, other related pathologies, such as pleural thickening, underlying lung diseases and non-respiratory diseases may contribute to breathlessness [4]. Chest pain can be pleuritic or non-pleuritic in character. Pleuritic chest pain may be localized or referred. The pain is usually sharp and is exacerbated by movement of the pleural surfaces, as with deep inspiration, coughing, and sneezing. Excess pleural fluid can directly cause chest discomfort. Chest pain can also arise from malignant infiltration of the chest wall [4,5].

Cough is also common and can be due to associated lung disease but is directly related to the effusion itself through other mechanisms such as airway irritation from the collapsed lung [6].

2.3.2. Physical signs

The physical signs may vary with the amount of fluid accumulated. In large effusion, there will be classical signs of fullness of intercostal spaces, reduced movement of the affected side and dull percussion note. Auscultation reveals not only reduced breath sounds but also decrease in tactile and vocal fremitus. Egophony can be pronounced near the upper margin of the effusion. Pleural rubs, often mistaken for coarse crackles, can be heard during active pleurisy without any effusion

or with minimal effusion. Physical signs of the underlying pulmonary or systemic causes of the effusion may be detected [7].

2.4. Further course of action after initial clinical evaluation

Pleural effusion is evaluated to elucidate the underlying causes and to guide at least the initial management. Clinical history and physical findings could not only diagnose the pleural effusion but may also hint the etiology of effusion. A history of cardiac, renal, or liver impairment can suggest transudative effusion. Physical features of these diseases support the type of effusion shown by pleural fluid analysis. Older age, weight loss, and a history of smoking may suggest a possibility of malignant pleural effusion. Recent leg swelling or deep vein thrombosis may result in an effusion related to pulmonary embolism. Low grade fever, loss of appetite and decreased weight over some time may suggest a smoldering infection like tuberculosis and a systemic disease as the cause of effusion [7].

2.4.1. Imaging

Chest X ray

Straight chest X rays are useful to confirm the presence of effusion. The findings of effusion vary with the amount of pleural fluid. Effusion is usually only detectable when the volume is >200 mL, obliterating the costophrenic angle on an upright posteroanterior (PA) view [8]. Classically, a homogenous opacity is seen with obliteration of the costophrenic angle and a curved upper border, 'the meniscus sign'. Atypical radiological findings may be observed in loculated effusions, which could be in lateral (lamellar), mediastinal, apical, subpulmonic, or fissural sites. Fissural loculations are biconvex opacities, mimicking a mass, are seen (most commonly) in congestive heart failure, and disappear after treatment. Resolving pleural effusions sometimes give rise to a rounded opacity due to peripheral atelectasis, commonly located basally and dorsally [9].

Radiographic clues suggestive of a subpulmonic effusion are apparent elevation of the ipsilateral diaphragm; movement of the apex of the hemidiaphragm from the medial to lateral third; flattening of the medial aspect of the diaphragm; no visualization of the lower lobe blood vessels below the diaphragm; and the distance from the apparent diaphragm to the fundal gas is increased in the left subpulmonic effusion. Lateral decubitus radiography is valuable for evaluation of a subpulmonic effusion, unless it is encysted [9].

Thoracic ultrasound

Even small amounts of pleural effusion can be detected by ultrasonography. Moreover, thoracic ultrasound (TUS) could estimate the amount of pleural fluid and guide the site for thoracentesis [7]. The ultrasonographic image of pleural effusion is characterized by an echo-free space between the visceral and parietal pleura. TUS is also helpful in distinguishing between fluid-filled and solid lesions and can confirm the presence of effusion in cases of loculated and subpulmonic pleural effusion [9].

Computerized tomography

Computed tomographic (CT) scan chest is sensitive for detection of pleural fluid. On supine CT, fluid accumulates in the posterior and deep lateral pleural recesses8. Whilst CT scan may not be recommended as a routine part of evaluation of all patients with pleural effusion, it is highly useful in the evaluation of some diseases like malignant pleural effusions and pleural infections [10]. CT scan can be used to evaluate complex situations in which the anatomy cannot be fully assessed by plain radiography or TUS [9].

2.4.2. Thoracentesis and pleural fluid analysis

Most of the unilateral effusion in adults needs thoracentesis to determine the cause of pleural fluid unless there are strong indications suggestive of extrapulmonary systemic cause. Aspiration is required for bilateral effusions in clinical settings where it is essential for evaluation or is used as a therapeutic procedure for breathlessness. The fluid obtained undergoes biochemical, cytological, and microbiological examinations to establish the cause of effusion [9].

Pleural fluid biochemistry is one of the key tests in the pleural diagnostic pathway. The first step in the evaluation of patients with pleural fluid is to distinguish those who have inflammatory (exudative) effusions from those who have non-inflammatory (transudative) effusions. **Protein content usually exceeds 3 g/dl in exudates**. Light's criteria can also be used for differentiating exudative from transudative effusion [11].

Light's criteria, suggest possibility of an exudative effusion when **any one** of the following results is found:

- a ratio of pleural fluid protein to serum protein higher than 0.5
- a ratio of pleural fluid lactate dehydrogenase (LDH) level to serum LDH level higher than 0.6
- a pleural fluid LDH level higher than 200 IU per liter (or >67% of the upper limit of the normal range for serum LDH level)

Clinical context needs to be taken into account in interpretation of marginal values. It is to be noted that Light's criteria may misclassify some transudates as exudates in patients who have underlying congestive heart failure and are receiving diuretic therapy [9,10].

Microbiological investigation, including culture and sensitivity, is an essential diagnostic component to determine causative organisms in non-tuberculous pleural infection and guide the antibiotic treatment [9,10].

Useful information obtained from pleural fluid analysis are differential cell count and cytological picture. The cell count can give clues for causes of effusion, and pleural fluid cytology is the essential first step in diagnosing malignant pleural effusion. Pleural biopsies taken by different methods (closed blind, image guided or visualized) will provide the essential information for final confirmation of the etiology [10].

Biomarkers

Pleural fluid adenosine deaminase (ADA), interferon gamma (IFN-γ), antinuclear antibody (ANA), N-terminal pro b-type natriuretic peptide (NT-proBNP) may be useful in some cases of effusion. For example, raised pleural fluid ADA level may support the diagnosis in tuberculous pleural effusion. Their roles are described in specific conditions.

Serum biomarkers are of little help except NT-proBNP, where cardiac failure is the likely cause of pleural effusion.

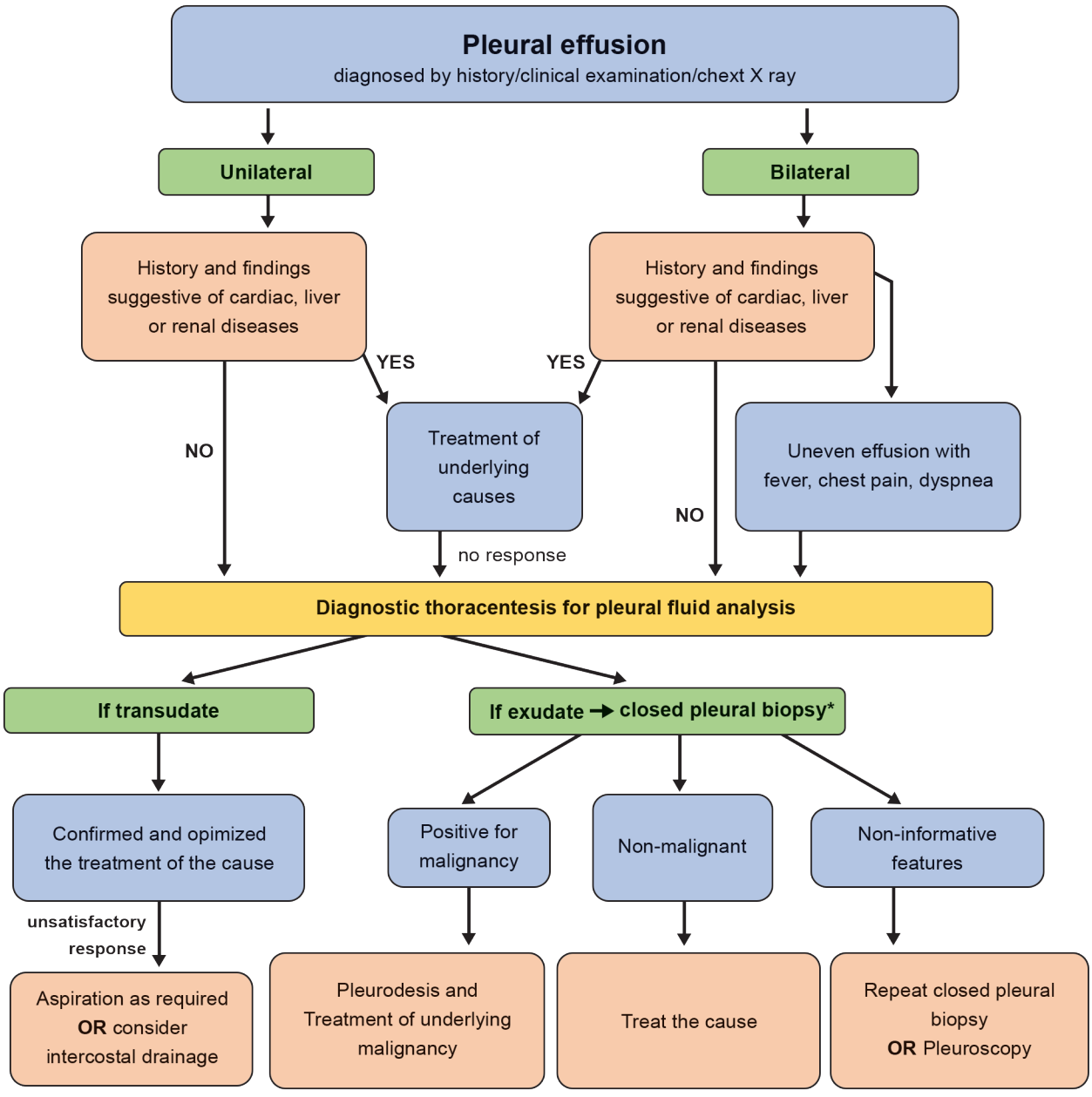
Detailed investigative procedures and findings are described in specific topics of effusion in the sections followed.

2.5. Management in general

Clinical evaluation, diagnostic thoracentesis plus pleural fluid analysis and histopathological examination of pleural tissue, if done, guide the clinician for further actions and management. Microbiological examination may have been done in appropriate circumstances. Therapeutic thoracentesis is required for symptomatic patients with effusion. Dyspnea often improves after

thoracentesis, irrespective of lung re-expansion and relates to the mechanics of diaphragmatic function [4,5]. Symptomatic treatments include pain relieving medication, cough suppressants, and nutritional supplements.

Specific management strategies are described in each section of different conditions.



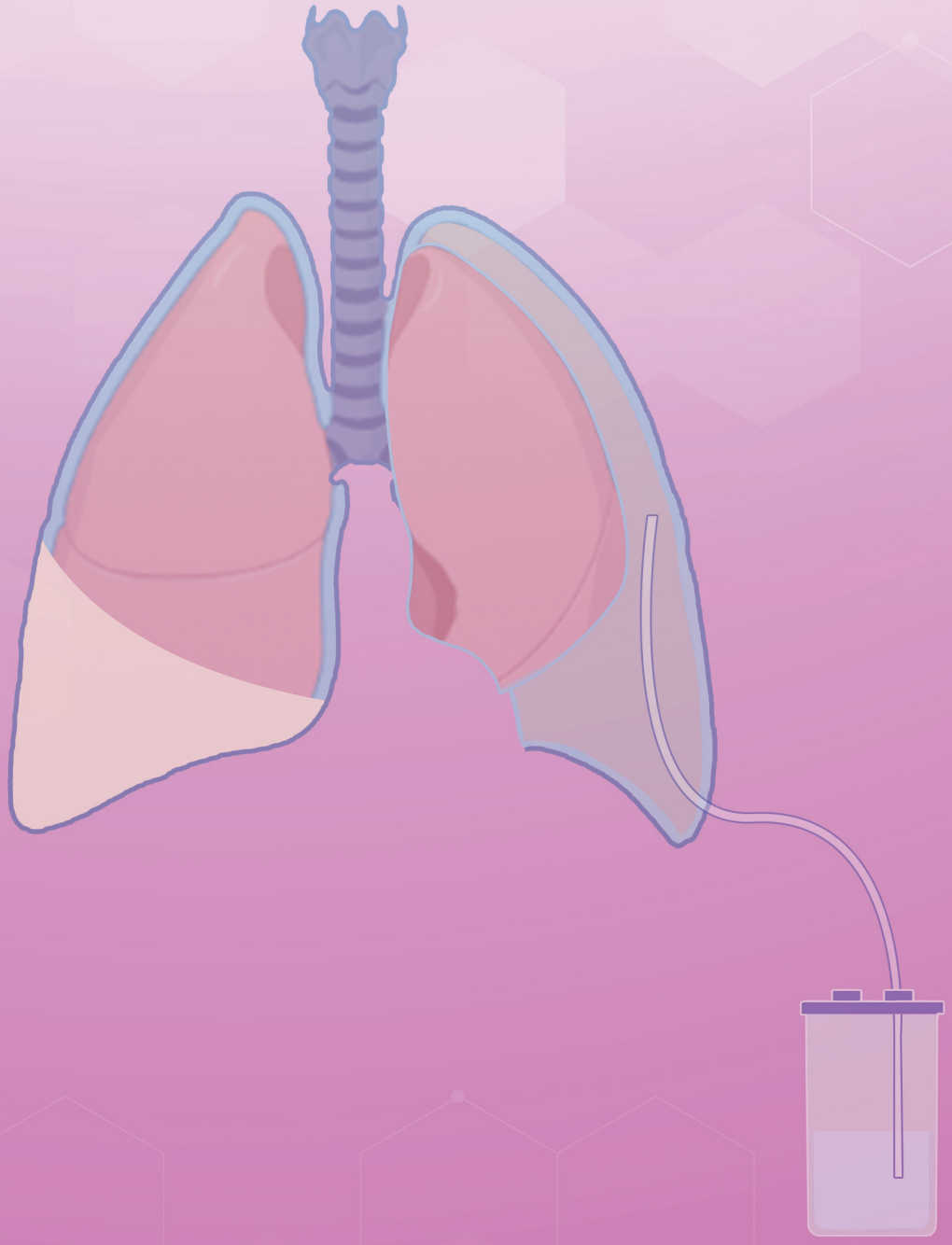
*If closed pleural biopsy is not available, features in pleural fluid cytology and biological appearances may help to reach the diagnosis.

Figure 2. A logical approach to a patient with pleural effusion

Highlight points

- Transudative pleural effusion is mainly due to increased hydrostatic pressure or decreased oncotic pressure while exudative effusion is caused by increased mesothelial and capillary permeability or impaired lymphatic drainage at the pleura.
- Evaluation of pleural effusion starts with clinical history and physical findings getting clues to possible etiologies. A wide range of further investigations including pleural fluid analysis, microbiological studies, imaging, histopathological examination of pleura, and biomarkers in some cases are required. The intensity of the investigation will vary case by case.

3 Pleural Infections



3. Pleural Infections

Pleural effusion develops in pneumonia up to 50% of patients and, the occurrence of pleural effusion can be associated with a 3-6-fold increase in mortality of them [12]. A parapneumonic effusion (PPE) is a pleural effusion that occurs in patients with concurrent lower respiratory tract infection or pneumonia. It is an exudate and can create a new and different infected area that accompanies and often worsens the ongoing parenchymal disease [13].

While the majority of these simple parapneumonic effusions resolve with antibiotics and optimal medical therapy, approximately 15% progress to bacterial invasion of the pleural space and become "true pleural infection". Pleural infection denotes bacterial entry and replication in the pleural space [13] – the terms "complicated" and "uncomplicated" parapneumonic effusion have been used. The "empyema" refers to the macroscopic detection of purulent pleural fluid and represents one end of the spectrum of pleural infection. In this guideline, the term "pleural infection" is used to include both empyema and "complicated" para-pneumonic effusion (CPPE) [14].

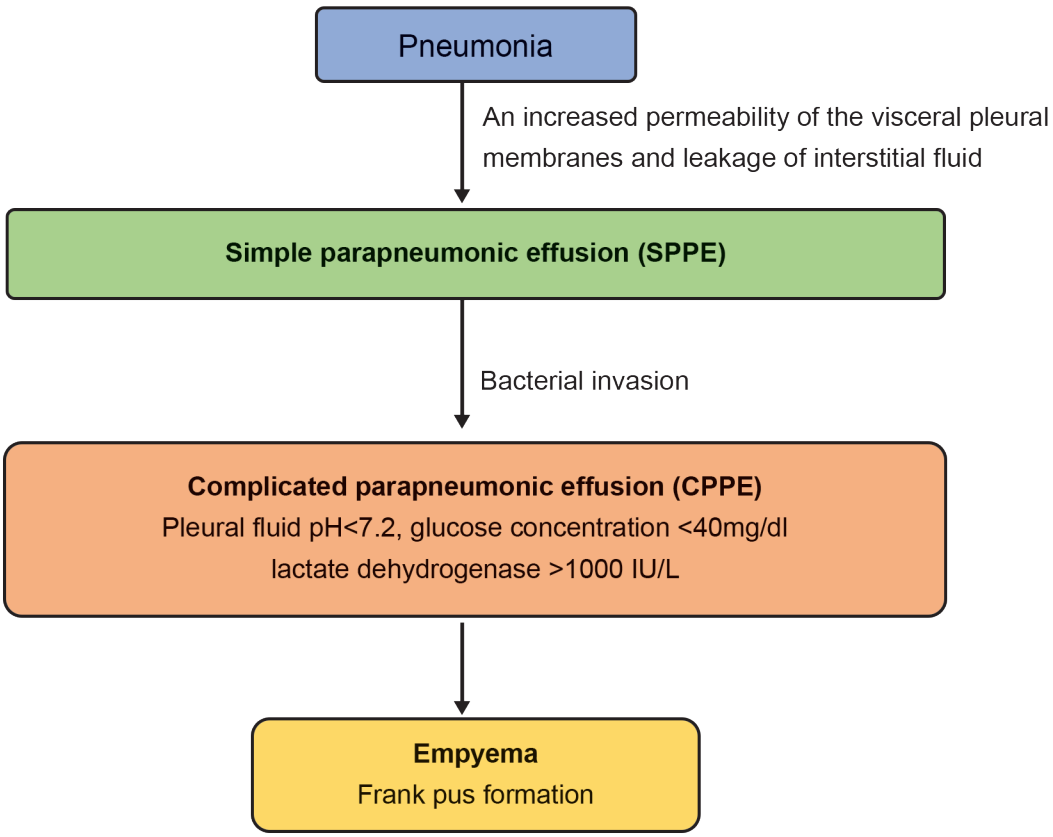


Figure 3. Progression of parapneumonic effusion to empyema

3.1. Parapneumonic effusions

Parapneumonic pleural effusions vary in amount from a very small effusion, barely visible on the chest X ray, to a large effusion causing significant ventilatory compromise.

3.1.1. Predisposing factors

Predisposing factors include diabetes mellitus, immunosuppressive states (acquired through diseases such as HIV infection or induced iatrogenically by treatments like corticosteroids/ immunomodulatory/ chemotherapeutic agents), gastro-esophageal reflux, malnutrition, alcohol misuse and intravenous drug abuse. A history of aspiration or poor oral hygiene is often elicited in anaerobic infections. It can also follow pleural interventions, thoracic or esophageal surgery and trauma [17, 18]. Concurrent hidden malignancy may be considered in patients with a prolonged clinical course [18].

3.1.2. Microbiological spectrum

Most of the community-acquired pleural infections are caused by Gram positive aerobic organisms, especially streptococcal species, and Staphylococcus aureus. Gram negative bacteria are less commonly found in community-acquired disease, but anaerobic bacteria are often seen both in isolation and as co-infection with aerobic organisms.

Hospital-acquired pleural infection is dominated by resistant Gram-positive organisms (including methicillin-resistant Staphylococcus aureus (MRSA)) and Gram-negative organisms such as E coli, Enterobacteria and Pseudomonas, with a significant anaerobic involvement. Poly-microbial infection is seen in both community and hospital-acquired disease, especially detected when molecular diagnostic techniques are used [19].

In our community setting Mycobacteria tuberculosis is one of the most common organisms causing infective pleural effusion in immunocompetent as well as in immunocompromised patients. Fungal pleural infection is rare (less than 1% of cases), usually seen in immunosuppressed individuals, and is associated with a high mortality.

Seasonal variation in incidence of pleural infection and a temporal association with influenza was noted. However, a direct causative role of viruses in the pathogenesis of pleural infections has yet to be elucidated [20].

3.1.3 Pathophysiology

The majority of pleural infections is thought to be the result of the formation and evolution of a parapneumonic effusion across three progressive stages.

1. The direct invasion of micro-organisms in the lung parenchyma leads to breakdown of host defenses and provocation of intra-alveolar exudates.
2. The resultant parenchymal inflammation causes an increased permeability of the visceral pleural membranes and leakage of interstitial fluid.
3. The mesothelial cell lining is further disrupted by neutrophil migration and pro-inflammatory cytokines, including tumor necrosis factor-α (TNF α), interleukin (IL)-6 and IL-8, released by pleural mesothelial cells into pleural space [20].

Anatomical distortion of the visceral pleural mesothelial lining creates intercellular "gaps" and increasing permeability, allowing accumulation of pleural fluid [21]. This initial exudative phase causes **simple parapneumonic effusions,** with no detectable bacteria and hence have a glucose level similar with blood with no acidity (pH>7.2). Prompt antibiotic therapy at this stage will result in resolution of the effusion [22].

The mechanism by which secondary bacterial invasion of the pleural space occurs is incompletely understood. Spread from lung parenchymal consolidation, direct infection to pleural space via percutaneous route (mostly iatrogenic in the latter) and hematological seedling are possible ways by which microorganisms reach to the pleural space. As bacteria multiply, various changes occur within the pleural space, resulting in a **complicated parapneumonic effusion**. Bacterial metabolism and neutrophil phagocytic activity result in the production of lactic acid and carbon dioxide, causing in turn a decrease in pleural fluid pH and glucose concentration. These two features are pleural fluid markers for CPPE [23].

3.1.4. Diagnosis

Fever and rigors in the presence of an effusion in the context of a non-resolving pneumonia strongly suggest the development of CPPE [17,18,23]. The diagnosis of parapneumonic pleural effusion can often be delayed and challenging with clinical awareness being the key to recognize. Special alert is warranted in the elderlies, who may present with a more indolent illness showing only malaise, anorexia and weight loss [17]. The clinical diagnosis is confirmed by imaging and pleural fluid analysis.

3.1.4.1. Imaging

Imaging techniques include straight chest X ray, thoracic ultrasound (TUS) and computerized tomographic (CT) scan of the chest.

Chest X ray

Plain chest X ray could detect the pleural effusion and features of consolidation may still be visible. Pleural-based densities may suggest pleural fluid loculation in chest X ray [17,23].

Thoracic ultrasound

TUS is not only vital for guiding the safe sampling of the pleural fluid but may also identify features of pleural infections. Main features of TUS include the presence of echogenic swirling (often signifying exudate or pus) and fibrin strands seen as septations or fully enclosed loculations [24]. Detection of CPPE is better with TUS than straight chest X Ray and may even surpass CT scan in some cases [25].

Computerized tomography

The CT signs regarded to be typical for CPPE/empyema include thickening and enhancement of the parietal pleura, increase in the thickness and attenuation of the adjacent extrapleural fat, and enhancement of both the visceral and parietal pleura (split pleura sign), presence of multiple bubbles in the effusion (signifying anaerobic gas producing bacteria), and pleural septations [26].

CT scan features that are more common in pleural infection (parapneumonic, empyema and tuberculosis) than in malignancy are: [14, 15]

1) Lentiform configuration of pleural fluid, laterally or medially
2) Visceral pleural thickening (“split pleura sign”)
3) Hypertrophy of extra-pleural fat (>2 mm)
4) Increased density of the extra-pleural fat
5) Presence of pulmonary consolidation

A scoring system had been proposed using pleural contrast enhancement, pleural microbubbles, increased attenuation of extra-pleural fat and pleural fluid volume >400 ml, for identification of complicated parapneumonic effusion (CPPE) [16].

3.1.4.2. Pleural fluid analysis

Pleural fluid analysis provides the correct diagnosis and guides the appropriate subsequent intervention. In the presence of a clinical history or biochemical picture compatible with infection, a pleural fluid pH <7.2 [or] a combination of glucose concentration <40 mg/dL (2.2 mmol/L) with a lactate dehydrogenase [LDH] >1000 IU/L, are the most important predictors for chest tube drainage [27]. Neutrophil phagocytic activity, with protease production and cell wall lysis, leads to a fall in pH of the pleural fluid and concurrent fall in glucose, both characteristic biochemical features of complicated parapneumonic effusions [23,27]. While most cytological examinations of pleural infection fluid will show acute inflammation with neutrophilic predominance, it should be noted that early antibiotic administration can convert pleural fluid characteristics into a lymphocyte predominant picture [28].

3.1.4.3. Microbiological study

The presence of microbes shown by gram-stain and/or culture of pleural fluid proves pleural infection, but such investigations have a yield of <50% only in most studies. Inability to show microbes, therefore does not exclude infections [29]. Routine blood cultures have even a lower yield, about 12% with intrapleural sepsis. The microbiological yield can be substantially increased by the culture of pleural tissue taken with ultrasound guided biopsies. Pleural fluid fungal cultures are considered in suspected cases [30].

Nucleic acid amplification testing (NAAT) on pleural fluid specimens has shown a potential for a rapid (a few hours) and precise identification of microorganisms, particularly when patients have received antibiotics, or an anaerobic infection is suspected. The standard method involves polymerase chain reaction (PCR) amplification of the 16S rRNA gene (conserved regions common to all bacteria), followed by sequencing and comparison to known databases for genus and species identification. Whether identification of nucleic acid components in the absence of cultural growth of organism denotes an infective state is still debatable. The diagnostic usefulness of NAAT awaits multifaceted larger studies [31].

3.1.4.4. Blood tests

The following are hematological indicators for infections: [30]

- White cell count (>15×10^9/L)

- C-reactive protein (>100 mg/L)
- Platelet count (>400×10^9/L) and
- Low albumin (<30 g/L)

These hematological changes could support the diagnosis of pleural infections in an appropriate clinical context.

3.1.5. Management

Standard management for parapneumonic effusion includes antibiotic therapy, pleural fluid drainage and supportive measures.

3.1.5.1. Antibiotic therapy

Initial antibiotic treatment for suspected or confirmed pleural infection should commence before results of culture and sensitivity tests are available and will be dictated by the likely source of infection (community or hospital-acquired disease) which could suggest the likely microbiological spectrum. All patients should receive antibiotics targeted to treat the common bacterial profile of pleural infections and it should reflect local antibiotic policies and resistance patterns [17]. Antibiotics to cover anaerobic infection should be used in all patients except those with culture proven pneumococcal infection. Macrolide antibiotics alone are not used unless there is objective evidence for or a high clinical possibility of 'atypical' pathogens identified [14].

An empirical initial antibiotic choice in community-acquired pleural infection is a combination of Beta-lactam with anaerobic cover, whereas empirical treatment for hospital-acquired pleural infection should cover resistant Gram-negative organisms and MRSA [17](Table-2). A positive culture test from pleural fluid or blood may suggest the need for revision of empirical antibiotics. Antibiotic therapy is used for **two to six weeks** according to clinical response since the shorter courses may result in earlier clinical relapse [14].

Penicillin, penicillin combined with beta-lactamase inhibitors, metronidazole and cephalosporins penetrate the pleural space well. Quinolone could be administered via parenteral as well as oral route as it has a favorable pleural penetration. However, reasonable exclusion of tuberculous infection should be made before quinolone is used. Aminoglycosides have low pleural penetration

and a tendency to be inactivated in the acidic medium of the infected pleural space [23]. Non-liposomal formulations of antifungal therapy are preferred to liposomal due to their superior pleural penetration in patients with fungal pleural infection [32]. Intravenous antibiotics should be changed to oral therapy once there is clinical and objective evidence of improvement in sepsis. Intrapleural antibiotics are not recommended. Prolonged courses of antibiotics may be necessary and can often be administered on outpatient basis after discharge [14].

In general, choice of antibiotics is similar with the anti-microbiological treatment of underlying pneumonia, but the duration of treatment differs significantly.

3.1.5.2. Pleural fluid drainage

Small parapneumonic effusions can be managed without thoracentesis, although diagnostic sampling may be desirable to help the confirmation of diagnosis and identification of causative microbiological agents[33]. Optimal and timely drainage of infected pleural collections to achieve sepsis control continues to be the priority of care in pleural infection[34]. Removal of the chest drain is appropriate after radiological/ultrasonic confirmation of successful pleural drainage (reduction in the size of the pleural collection on the chest x-ray or thoracic ultrasound) and objective evidence of sepsis resolution (improvement in temperature and clinical condition and decreasing inflammatory markers e.g., C- reactive protein). Observation for 24 h before discharge from hospital, after drain removal is usual although a longer period of rehabilitation may be necessary as some patients may have been in hospital for a longer time than usual [14].

Patients with persistent sepsis and a residual pleural collection should undergo further investigations. These patients should seek the opinion of a thoracic surgeon to evaluate the need for concomitant surgical options (refer to empyema section).

3.1.5.3. Supportive measures

Supportive measures include adequate fluid intake, thromboprophylaxis if there is a risk, and nutritional support. as even when not always apparent, pleural infection represents a significant

Table 2. Empiric antibiotic regimen for parapneumonic pleural effusion

Type of infection	Target groups/ organisms	Suggested antibiotic	Alternatives (allergy, or local resistance patterns)
Community - acquired	Gram positive and negative aerobes	Penicillin with β-lactamase inhibitor (e.g., Ampicillin-sulbactam or Amoxicillin-clavulanate) ***(PLUS)***	Injectable 2nd or 3rd generation cephalosporin, - Cefuroxime - Ceftriaxone ***OR*** Quinolones - Moxifloxacin - Levofloxacin ***(PLUS)***
	Anaerobes	Metronidazole ***OR*** Clindamycin	Metronidazole ***OR*** Clindamycin
Hospital-acquired	Gram positive and negative aerobes (including Pseudomonas Species)	Antipseudomonal penicillin with β-lactamase inhibitor (e.g., Piperacillin-tazobactam) ***OR*** Carbapenem (e.g., Meropenem) ***(PLUS)***	Anti-pseudomonal cephalosporin (e.g., Ceftazidime, Cefepime) ***OR*** Quinolone (Moxifloxacin or Levofloxacin) ***(PLUS)***
	MRSA	Linezolid ***(PLUS)***	Vancomycin ***(PLUS)***
	Anaerobes	Metronidazole ***OR*** Clindamycin	Metronidazole ***OR*** Clindamycin

catabolic state [34]. Oxygen therapy and symptomatic treatment like pain relieving medications are given promptly whenever necessary.

3.2. Empyema

3.2.1. Introduction

Empyema thoracis can be defined as presence of pus and existence of microorganisms detected by Gram's stain or positive culture in the pleural fluid. It can occur mostly as a complication of intrinsic infection of the lung, namely bacterial pneumonia, with subsequent parapneumonic effusion or from extrinsic sources such as from chest wall and vertebra (injury, infection, surgery), mediastinum (esophageal rupture, anastomosis leak), sub-diaphragmatic pathology (subphrenic abscess, liver abscess) and hematogenous seedling of organism (septicemia) [35].

Patients at high risk include the young, the elderly, and those with intrinsic lung disease, mainly chronic obstructive pulmonary disease (COPD). In addition, diabetes mellitus, immunosuppression related to chronic corticosteroid use, gastroesophageal reflux, alcohol misuse, intravenous drug abuse, or poor oral hygiene are also possible contributing factors [36].

3.2.2. Microbiological spectrum

Common organisms encountered in empyema are similar with those found in parapneumonic effusion (see section 3.1.3).

3.2.3. Pathophysiology

The development of an empyema in association with pneumonia is a dynamic three-step process in which failure of treatment can escalate to the subsequent phase.

The "triphasic" nature of the disease was first described in 1962 by the American Thoracic Society: the whole process causing the development of an empyema takes about 4 to 6 weeks, revolving around progressive changes in the pleural cavity, appearance of the effusion, and the treatment given [35].

Three phases of empyema are **exudative, fibrinopurulent, organizing** phases.

3.2.3.1. Phase I: Exudative phase

The distinctive feature of this phase is a PPE characterized by the presence of clear, free-flowing fluid in the pleural space. Pathophysiology normally involves an altered balance between pleural fluid production and reabsorption due to inflammatory mechanisms, increased vascular and pleural permeability, and neutrophil chemotaxis. Most of these changes are due to increased production of proinflammatory cytokines (IL-8, TNFα). The pleural fluid is normally sterile, and the pH and glucose level are normal [37,38] (see more details in Section 3.1.3 – simple/uncomplicated PPE).

3.2.3.2. Phase II: Fibrinopurulent phase

In this phase the effusion progresses to development of septations and loculations. A fibrinopurulent empyema represents a complex pathologic process within the pleural space with variable presentation: the collection can be uni-loculated or multi-loculated involving most or the whole of

the pleural cavity. Septa are commonly present within the collection due to increasing fibrin deposit, activation of the coagulation cascade, and downregulation of the local fibrinolytic pathway. Micro-organisms are often present leading to chemical alteration of the pleural fluid (pH <7.2, Lactate dehydrogenase >1,000 U/L) and decreased glucose levels (<60 mg/dL) [37, 38].

3.2.3.3. Phase III: Organizing phase

An organizing empyema results in a thick, rigid pleural cortex. Pleural fluid turned into frank pus and fibroblast chemotaxis follows. The pleural thickening encases the lung causing fibrothorax leading to decreased ventilation and a perfusion–ventilation mismatch (restrictive syndrome) producing the symptom of dyspnea. This is the final stage of an untreated empyema. Bacteria are present, but this stage of the disease is non-reversible and functional impairment remains even after eradication of the infection [37, 38].

Table 3. Stage definition of pleural empyema (ATS) [39]

Exudative phase (stage I)	Fibrinopurulent phase (stage II)	Organized phase (stage III)
Inflammatory processes extend to the pleurae and result in immediate outpouring fluid	Frank pus accumulates especially laterally and dorsally	Thick and sedimented exudate
Low cell content	High cell content (PMN) and fibrin depositions over the pleural surfaces and fibrinous strands within the fluid	Fibroblast growth Fibrosis
	Tendency to loculations and formations of membranes	Tendency to loculations and formations of membranes
Re-expandable lung	Lung is less expandable	Trapped / non-expandable lung

3.2.4. Clinical presentations

The symptoms and signs of empyema vary according to the location of the infection and its severity. Aerobic pneumonic infections will tend to present with an acute febrile illness, localized pleuritic chest pain, sputum production and leukocytosis. Infections with anaerobes tend to lead a more

insidious clinical course with less pronounced fever and more generalized systemic symptoms, such as poor appetite and weight loss; such infections are more common in those with poor dental hygiene, in alcoholics and in those who have had a period of unconsciousness leading to aspiration of gastric contents [38].

Possibility of pleural infection should be considered in all patients with pneumonia, particularly in those who fail to respond to appropriate antibiotic therapy, as indicated by persistent fever, leukocytosis and raised inflammatory markers such as C-reactive protein. Immunosuppressed hosts and the elderly can present with disproportionately mild symptoms in relation to the severity of the pleural infection [38].

3.2.5. Investigations

Investigations comprise of imaging procedures and pleural fluid analysis including culture and sensitivity tests.

3.2.5.1. Imaging

Chest X ray

Chest X ray (PA) is recommended for any patient presenting with severe pneumonic symptoms, or those who are failing to respond to appropriate therapy for a respiratory tract infection. It shows a pleural-based opacity that obscures the hemidiaphragm and appears as a hazy or opaque area. Empyema forms an obtuse angle with the chest wall, due to their loculated orientation which are much larger in one projection (e.g. frontal) compared to the orthogonal projection (e.g. lateral) [40].

Thoracic ultrasound

TUS is recommended for any evidence of pleural fluid in chest X ray. Some of features found in empyema are homogenous echogenicity, anechoic effusion with hyperechoic septation, pleural thickening and split pleura i.e. separation of the parietal, and visceral pleural by the fluid. Thoracic ultrasound increases the success rate and reduces the complications of thoracentesis. Patients with a complex septated sonographic pattern tend to have less successful outcomes, higher intensive care unit admission rate and a higher mortality [38].

Computerized tomography

CT scan of chest is recommended for evidence of any indication for surgery such as septations and loculations, formation of pleural cortex (see section 3.1.4.1).

3.2.5.2. Pleural fluid analysis

Pleural fluid analysis is essential to obtain the correct diagnosis and guide the appropriate subsequent treatment intervention. Chest tube drainage is required when pleural fluid analysis shows the following [29].

Presence of pus and detection of microbes by Gram's stain or culture in the pleural space

OR

Evidence of CPPE in pleural fluid

1. PH < 7.2
2. Pleural fluid LDH > 1000 U/L
3. Glucose <40 mg/dl

3.2.6. Management

Management of empyema usually involves both medical and surgical treatments. The measures aim to control the infection and to evacuate the infected material as early and completely as possible [40].

The general principles for the treatment of empyema are [35]:

(1) Treatment of the underlying cause - infection

(2) Removal of infected fluid and debridement (re-establishment) of pleural space

(3) Obliteration of dead space

(4) Achievement of re-expansion of the lung

(5) Supportive measures to improve patient's condition and prevent complications including physiotherapy, nutritional support, etc.

Practical management of empyema can vary with the stage of the disease found at the time of diagnosis.

3.2.6.1. Management of Acute (Exudative) Phase of Empyema

It includes the followings:

Antibiotics

It is recommended to give according to culture and sensitivity test results if available. Before culture and sensitivity test result is available, appropriate empiric antibiotic therapy must be given. The intrapleural administration of antibiotics has no role in management of empyema [40]. Duration of antibiotics therapy is influenced by the organism, adequacy of source control and clinical response [30,35]. Details of antibiotic therapy are described in the parapneumonic effusion section (see table 2).

Evacuation of pleural fluid / drainage

Aspiration

Aspiration is a useful tool in the management of uncomplicated pleural effusion and is also an essential step in the diagnosis of complicated effusion [40]. Recommended size of needle for aspiration is 16 - 18 G.

Chest drain placement

Traditionally, large-bore chest drains have been used to drain pus or viscous fluid. Patients treated with a range of chest drain sizes (from >10F to <20F) showed no difference in primary and secondary outcomes (death, need for thoracic surgery, length of stay, chest X ray response and lung function at 3 months). The use of large-bore chest drains was associated with more pain [41]. Hence, small-caliber chest drain placement is preferred in the treatment of early stage, minimally septated empyema. Recommended drain size starts from 14 Fr caliber.

There is concern that smaller bore chest drains tend to become occluded with fibrin or pus. Care is usually taken to ensure that all the fenestrations on the chest drain are located intrapleural space to work effectively and minimize risk of infected fluid leakage into subcutaneous tissue [30].

Intrapleural therapy

Intrapleural treatments have been used for many years as an attempt to reduce/resolve septations and improve drainage, thereby aiming to avoid the need for more invasive surgical management. Intrapleural therapies include fibrinolytics, combined interpleural enzyme therapy, saline irrigation and intra-pleural antibiotics [37].

Fibrinolytic agents

Intrapleural fibrinolytics (using streptokinase/ urokinase) is not recommended for complicated pleural effusions and early empyema [14].

Interpleural enzyme therapy

The combination of intrapleural tissue plasminogen activator (t-PA and DNase) produced a clinical improvement in pleural drainage and a reduction in hospital stay in patients with empyema. In addition, the need for surgical intervention is reduced up to 75% at 3 months. However, treatment with DNase alone or t-PA alone is ineffective [42].

Intrapleural saline irrigation

Intrapleural saline irrigation may be useful in the management of pleural infection, but further studies are required in larger multicenter andomized control trial (RCT) settings [30].

Intra-pleural antibiotics

Direct administration of antibiotics may have the theoretical advantage of reducing systemic side effects and antibiotic resistance. However, the efficacy of intrapleural treatment may be hampered by non-uniform distribution across septated or multiloculated pleural spaces. There is **currently no evidence** for the role for intrapleural antibiotics in the routine management of pleural infection [30].

3.2.6.2. Management of Fibrinopurulent phase of empyema

These involve the following:

Antibiotics treatment

It is likely to be continuation of antibiotic therapy of exudative phase.

Surgery

Surgery should be considered without delay in patients who fail to improve with antibiotics and chest tube drainage, and who have persistent infective symptoms (fever, leukocytosis and raised inflammatory markers). The main modalities of surgical management include drainage, de-loculation, debridement and obliteration of the pleural space, ideally by decortication [37, 40]. There are two main

surgical approaches:

1. Video-assisted thoracoscopic surgery
2. Thoracotomy

Video assisted thoracoscopic surgery

Video assisted thoracoscopic surgery is the preferred approach for all patients with stage II empyema. It is used for removal of septations followed by chest tube (28 Fr size) drainage. It is recommended in all patients with stage II acute empyema in which there are TUS or CT proven septations or loculations. VATS is the procedure of choice, as it is equally effective but less invasive (and hence results in shorter hospital stay and fewer complications), compared to clearance by thoracotomy in both adults and children [43].

Despite being minimally invasive, decortication via VATS is associated with a 30-day post-operative mortality ranging from 2% to 6%, as well as with a complication rate varying from 9% to 40% [44]. The main complications include pain, prolonged air leaks, bleeding, recurrence or persistence of the disease, infection of the surgical wound and a residual pleural space [45].

In several retrospective studies, those referred late for surgery had more complications and had less favorable outcome with VATS [40].

Thoracotomy

Thoracotomy should be the approach when there is uncontrollable bleeding, injury to structures not amenable to thoracoscopic repair, and intolerance of single lung ventilation. The need for approach by thoracotomy should also be seriously considered when approach by VATS is not producing satisfactory evacuation with resultant unsatisfactory re-expansion of the lung [40].

3.2.6.3. Management of chronic organizing phase of empyema

In this stage, the turbid thick fluid of stage II begins to organize and forms granulation tissue. The granulation tissue and the underlying inflammation leads to formation of a thick fibrous layer covering the visceral pleural surface. The principle of treatment of this chronic state is surgical intervention as pleural drainage procedures are no longer effective. Effective surgical treatment

entails removal of purulent collections and debridement of infected tissue followed by obliteration of the empyema space to prevent recurrence. The choice of the initial approach is dictated by the condition of the patient, pleural space, and state of underlying lung parenchyma [40].

Antibiotics treatment

Antibiotic therapy in combination with surgical treatment is likely to be based on the same principle as that of parapneumonic pleural effusion. It is no longer a predominant necessity and is rather considered as an adjunct to surgical management.

Surgical procedures

Decortication involves peeling off the granulation tissue and/or fibrous layer overlying the visceral and at times parietal pleura to allow for expansion and aims also for debridement of infected tissue. Frankly necrotic lung parenchyma can be resected if warranted38. Extensive resections are to be avoided as much as possible because bronchial stumps in infected fields are prone to form fistulae. If bronchopleural fistulas (BPFs) are present, they should be closed if possible [40]. Persistent empyema refractory to standard therapies, including VATS, can be considered for open window thoracostomy (OWT) with prolonged chest tube drainage or decortication [35].

3.2.7. Risk scores for outcome prediction

Outcome prediction scores used in sepsis (qSOFA: quick sepsis-related organ failure assessment) and pneumonia (CURB-65) perform poorly in pleural infection. The RAPID score was postulated in 2014 as the first specific prognostic risk model. Baseline serum urea (renal), patient's age (age), pleural fluid purulence (purulence), infection source (hospital versus community infection) and serum albumin (dietary) are independently associated with mortality at 3 months for patients with pleural infection [46] (see annex: Table 6).

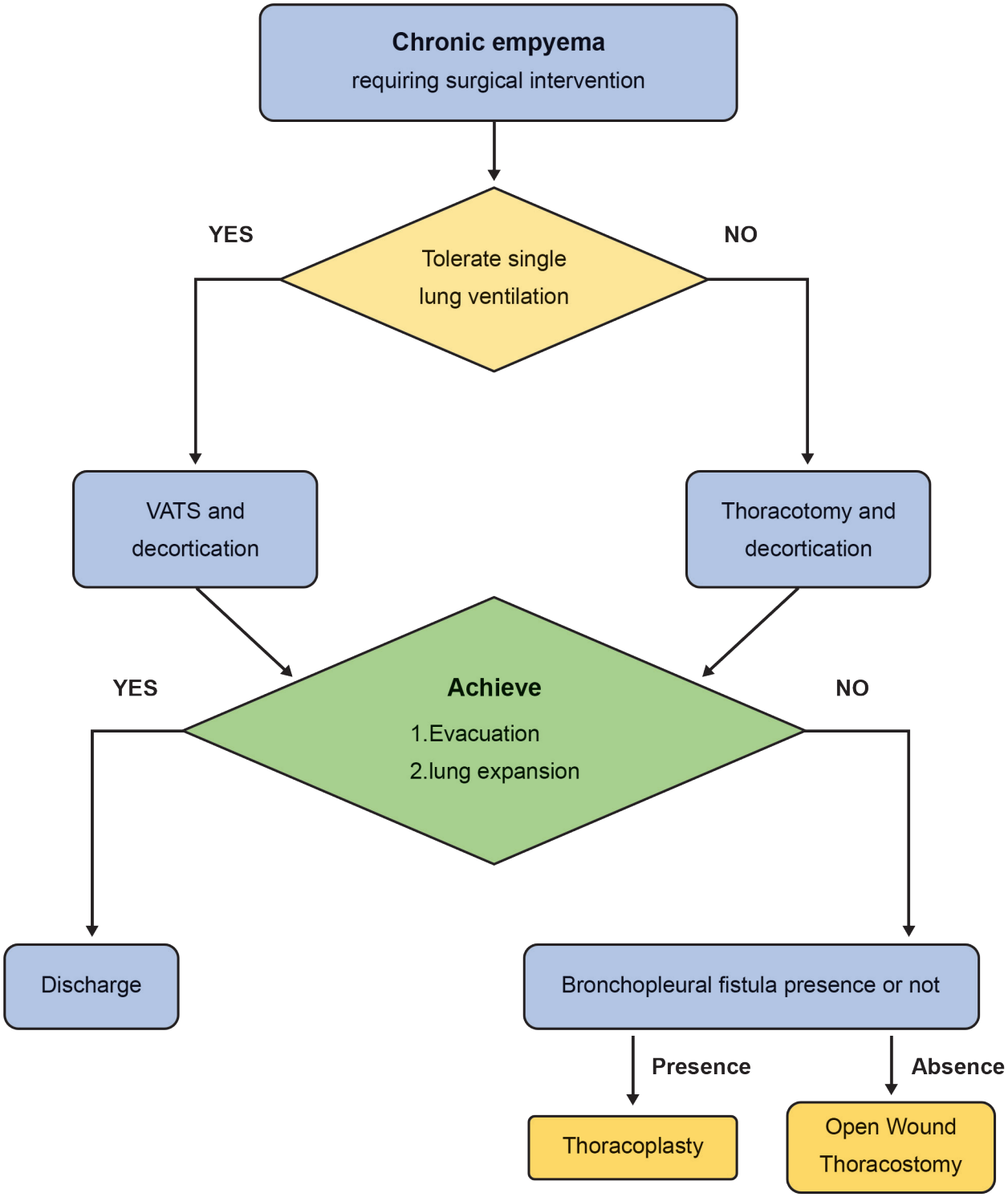


Figure 4. Management flow chart for chronic empyema

3.3. Tuberculous pleural effusion

3.3.1. Introduction

Tuberculosis (TB) is caused by Mycobacterium tuberculosis complex, and it is one of the leading causes of morbidity globally. Tuberculous pleural effusion (TPE) is the second most common form of extrapulmonary TB after lymph node TB [47]. Among immunocompetent patients, extrapulmonary TB accounts for 15%–20% of the total TB cases, while in patients with human immunodeficiency virus (HIV) infection, this proportion can be as high as 50% [48]. TPE is a disease entity with a spectrum of presentations. It may be a largely simple exudative effusion, which resolves completely with or without treatment, or a complicated effusion with loculations, pleural thickening and even frank empyema, resulting in a lasting effect on lung function in all patients with the latter condition [49].

TB-related pleural effusions may also present as cholesterol effusions (pseudo-chylothorax) and Chylothorax [50].

3.3.2. Pathophysiology

3.3.2.1. Tuberculous pleuritis and effusion

TB pleuritis is a form of a delayed hypersensitivity reaction triggered by the presence of Mycobacteria tuberculosis (Mtb) bacilli in the pleura and the pleural space. It occurs 6–12 weeks after a primary infection or in the process of reactivation of TB. In the absence of overt parenchymal disease, Mtb is believed to access the pleural space following the rupture of a small subpleural caseous focus. The initial inflammation leads to increased capillary permeability and increased pleural fluid formation. An early predominance of polymorphonuclear leukocytes characterizes the cellular component, followed by a macrophage influx, peaking after three days, at which time a lymphocyte-predominant effusion commonly develops [51]. This lymphocytic recruitment leads to an intense T-helper type 1 (TH1) cell-mediated delayed hypersensitivity reaction to Mtb. The TH1-driven immune response releases adenosine deaminase (ADA) and interferon-gamma (IFN). Monocyte-macrophages are responsible for granuloma formation that help to isolate organisms and prevent their dissemination [52]. Lymphocytic infiltration and granulomatous involvement of the pleura precipitates occlusion of lymphatic stomata and consequent reduction in pleural fluid clearance.

The difficulty of obtaining positive culture, even from large volume of fluid is attributed to the paucibacillary nature of the effusion, might be explained by an intense immune response leading to considerable bacterial clearance in TPE. This process may be the reason that most TB pleuritis cases have a benign clinical course [50].

3.3.2.2. Tuberculous empyema

TB empyema is a chronic active infection of the pleural space resulting in purulent pleural fluid with a high mycobacterial load. It is far less common than TB pleuritis and has a different pathogenesis. The postulated mechanisms through which a TB empyema may develop include [50]:

1) spillage of caseous material from a cavity or other parenchymal focus through a bronchopleural fistula
2) direct extension of infection into the pleural space from thoracic lymph nodes or a subdiaphragmatic focus
3) progression of a large primary tuberculous pleural effusion (with perhaps inadequate immune response)
4) hematogenous spread of Mtb to pleura
5) following surgical treatment of pulmonary TB (e.g. pneumonectomy).

3.3.2.3. Tuberculosis related lipid effusions

TB-related cholesterol pleural effusions are normally associated with a protracted course of untreated pleural TB resulting in thickened pleural membranes and a trapped lung. It is postulated that erythrocytes and neutrophils 'trapped' in the pleural space release cholesterol and other lipid constituents from degenerating cell membranes. The resultant effusion is cloudy and known as pseudo-chylous effusion [51,53].

TB can cause nontraumatic obstruction or dysfunction of the flow of chyle through the thoracic duct, leading to a true chylothorax. It may develop primarily or secondarily to immune reconstitution syndrome. Majority of cases have pathological mediastinal lymphadenopathy at presentation (causing occlusion or erosion into the thoracic duct and leakage of chyle into the pleural space), Uncommonly erosion of thoracic duct by spinal abscesses can be the underlying cause [54].

3.3.3. Clinical presentations

3.3.3.1. Tuberculous pleuritis and effusion

The usual age of onset may vary, and patients tend to be younger in regions of high TB prevalence. TB pleural effusions typically present as acute to subacute illnesses, characterized by unilateral pleuritic chest pain, cough, fever, night sweats, dyspnea and weight loss. A small proportion of patients have only mild symptoms. The PLHIV tends to present more frequently with associated

disseminated TB, lymphadenopathy and hepatosplenomegaly, a longer duration of illness, milder chest pain and a higher rate of systemic features such as loss of weight and night sweats [49].

Most TB pleural effusions tend to undergo spontaneous resolution within 2–4 months of onset. However, historic data show that up to 60% of patients with pleural TB will develop pulmonary TB within 5 years if no proper anti-TB treatment was given [55]. Residual pleural thickening (RPT) is the most common long-term sequelae of TB pleuritis. RPT of >2 mm was seen in 50% of chest X ray and 60% of chest CTs from patients with resolved pleural TB. Fibrothorax, where the lung is encased by a uniformly thickened pleura of >10 mm, has also been reported [56].

3.3.3.2. Tuberculous empyema

TB empyema may present with a paucity of symptoms and may even be incidental findings on routine chest X ray. Occasionally, the first presentation is that of empyema necessitatis, when the purulent material extends through the parietal pleura into the chest wall, often draining onto the skin forming fistulae [57].

3.3.3.4. Tuberculosis related lipid pleural effusion

Patients with pseudo-chylothorax usually present with insidious onset of dyspnea. More often than not, they are usually found out in a work-up of an apparent empyema thoracis [58].

3.3.4. Diagnosis

The definitive diagnosis of TPE requires demonstration of Mycobacterium tuberculosis in the sputum, pleural fluid, or pleural tissue [58]. The probable, and clinically confident, diagnosis can also be established by finding a histological picture of a typical caseating granulomas in the parietal pleura of patients with highly supportive clinical features. An elevated concentrations of adenosine deaminase (ADA) in a high-incident area or unstimulated interferon-γ in pleural fluid strongly suggest the diagnosis of TB etiology [59].

3.3.4.1. Pleural fluid analysis

Cellular composition

TB pleural effusion shows a predominantly lymphocytic (<50%) cells in an exudate. Neutrophils may predominate in the first few days of the effusion. When a frank empyema develops, the effusion may revert to neutrophil predominance. Culture is frequently not positive [49] (See below).

Pleural fluid ADA

It could be a valuable tool to the clinician, with a high overall diagnostic sensitivity of 0.92 and specificity of 0.90 [61]. In our local setting an ADA value of 42.5 IU/L carries a positive predictive value (PPV) of 96% and a negative predictive value (NPV) of 83%. The area under curve (AUC) that represents the diagnostic accuracy is 0.96 (i.e., unsatisfactory in ruling out TB) [60].

There is a potential for a false positive result in bacterial pleural infection, chronic rheumatoid effusions, mesothelioma, lung cancer and hematological malignancies where use of the ADA-2 isoenzyme assay can increase the test's specificity for TB. TPEs are unlikely to have an elevated ADA of >250 IU/L. In these instances, bacterial empyema or lymphoid malignancy should be considered. An LDH to ADA ratio of <16.2 suggests TPE with a high degree of accuracy [62]. Its diagnostic usefulness is likely to be significant in high TB prevalence communities where differential diagnoses are limited in number. Hence, it should be interpreted in conjunction with clinical and other parameters.

Pleural fluid IFN-γ

IFN is a cytokine that plays an essential role in T-cell-derived granulomatous inflammation and has been investigated as a marker for TPE diagnosis [63]. Assays that directly quantify the amount of IFN-γ in pleural fluid (so-called 'unstimulated' IFN-γ) have a high sensitivity (89%) and specificity (97%) for tuberculous effusions and may be superior to ADA [51].

Microbiological examination of pleural fluid

Conventional smear microscopy with Ziehl–Nielsen or Auramine stains of pleural fluid has a low yield of <10%. TB empyema, loculated effusions and effusions in HIV-positive people represent the populations with a higher mycobacterial load and thus a yield of up to 20% for smear microscopy [64].

The solid culture media such as Lowenstein–Jensen medium has a <30% yield. The newer liquid culture media such as the BACTEC-MGIT semi-automated system (Becton-Dickinson, Franklin Lakes, NJ, USA) yield higher positive results (up to 70%) with the additional advantage of shorter turn-around time [65].

Nucleic acid amplification tests (NAAT) are rapid molecular techniques that can detect small quantities of M. tb genetic material. A widely used polymerase chain reaction (PCR) method is the

Expert MTB/RIF platform (GeneXpert; Cepheid, Sunnyvale, CA, USA) which integrates with sample processing in a single self-enclosed test unit. Xpert MTB/RIF has a low sensitivity of 18.4% and specificity of 98.2%. but Gene Xpert Ultra increases sensitivity up to 50%. However, there is the possibility of a false-positive result (for the detection of both Mtb and of rifampicin resistance), particularly with the Ultra platform, in patients who have had previous TB66. If the risk for MDR-TB is high, microbiological examination of pleural tissue, to isolate the organism and establish the drug sensitivity profile, is highly desirable.

3.3.4.2. Interferon Gamma Release Assay

This test is used to identify patients who have been infected with Mtb (i.e. latent TB), but they are much less useful in diagnosing patients with TPE. IGRA performs poorly in the diagnosis of TPE, and there are low pooled sensitivity and specificity for blood and pleural fluid assays [68, 69]. Since IGRA test has high cost, highly variable diagnostic performance for active pleural TB and difficulty in interpretation, it is not recommended for diagnosis of TB pleural effusion [70].

3.3.4.3. Sputum and bronchoalveolar lavage

Sputum for identification of Mycobacterium is frequently done in cases with TB pleural effusion and it can be more useful in patients who have parenchymal infiltrates on chest X ray [49]. In those who do not produce sputum, bronchoalveolar lavage may be considered in selected cases. The Xpert® MTB/RIF is a rapid and automated molecular assay which is particularly useful for sputum examination.

3.3.4.4. Pleural biopsy

The biopsy of parietal pleura can be performed either as a closed blind procedure (with or without ultrasound guidance) or as a visualized procedure via pleuroscopy. The presence of caseating granulomas, identification of acid-fast bacilli or a positive TB culture in a pleural tissue specimen is sufficient for diagnosis of TPE [51, 58]. Non-caseating granulomas may also be caused by TB, especially in the early course of pathogenesis, and may contribute to diagnosis if the clinical probability is high. The sensitivity of pleural biopsy is 69–97% and tends to be higher in HIV-positive individuals. The technique used to acquire pleural tissue is often dictated by the local expertise and resource availability [49]. Pleural tissue produces higher yields than fluid in both Xpert platform and culture for Mtb in TPE [67].

3.3.4.5. Imaging

Chest X ray

In chest X ray, TPEs are commonly unilateral, without preference for the side, and vary significantly in size. The reported rates of concomitant parenchymal abnormalities on chest X ray in TPE vary from 20 to 50% [49,50,51]. Residual pleural thickening and lung encasement are possible long-term sequelae visible on chest imaging especially in patients who were delayed getting treatment or inadequately treated or untreated [49].

Thoracic ultrasound

Ultrasound findings are otherwise non-specific and may show free flowing anechoic pattern, complex echogenic pattern and septations/loculations [49]. TPE has a high protein content leading to fibrin strands and septations. The presence of loculations may increase the pretest probability of TPE [51]. However, loculations have not been shown to significantly differentiate between TPE and non-tuberculous empyema. The role of transthoracic ultrasound in TPE is primarily to guide investigations and interventions, maximizing the yield and improving safety [71].

Computerized tomography

CT scan of a patient with a TPE shows diffuse and the 'split pleura' sign. Concomitant parenchymal disease is more frequently detected (up to 80%). The most common findings are micronodules in the subpleural and peribronchovascular interstitium, and interlobular septal thickening [71].

3.3.5. Management

3.3.5.1. Anti-tuberculosis treatment

The chemotherapeutic treatment of TPE is the same as that used for pulmonary TB, with the standard regimen [49, 50, 51]. The 6-month regimen is divided into two phases: a 2-month initial phase of isoniazid, rifampicin, ethambutol, pyrazinamide (2HREZ), followed by a 4-month continuation phase of isoniazid and rifampicin only (4HR). Fixed-dose combination (FDC) formulations are usually recommended for treatment to improve compliance and to simplify drug delivery. One FDC tablet (for adults) contains Rifampicin (150 mg), Isoniazid (75 mg), Ethambutol (275mg) and Pyrazinamide (400 mg). Formulations for children is different. Combination is variable according to the phase used. FDC tablets are administered according to weight bands of patients.

Patients living with HIV/AIDS are treated similarly to those who are HIV negative, and ART should be started in all TB patients with HIV, regardless of CD4 cell count. In recently diagnosed HIV patients, TB treatment should be initiated first, followed by ART as soon as possible. Some ART medications may need dose adjustments or use of alternative ART regimen may be required [50].

In TB empyema or loculated TPE, however, it is often necessary to extend the duration of therapy. When the pleura is extensively thickened and calcified, the penetration of anti-TB drugs into the infected fluid is likely to be inadequate. Significantly lower maximum drug concentrations are attained, as well as there is a delayed rise to maximum drug concentration inside a TB empyema compared to serum drug levels [58, 65].

Pleural effusion due to drug-resistant TB should be managed according to the Myanmar guidelines for management of drug-resistant TB.

3.3.5.2. Corticosteroids

The use of corticosteroids in TPE is not standardized. It can be beneficial in selected patients who have severe systemic/local symptoms, after therapeutic thoracentesis. It should be given after at least two weeks of anti-TB treatment, and for a short period only (a few days or weeks). Corticosteroid use may produce possible reduction of the risk of residual pleural effusion, pleural adhesion and thickening [58].

3.3.5.3. Pleural fluid drainage

In symptomatic effusions, therapeutic thoracentesis relieves dyspnea rapidly, and is associated with a quicker resolution of fluid, reduction in residual pleural thickening and improvements in lung functions. Patients with loculated effusions are more likely to have residual pleural thickening with reductions in forced vital capacity [58].

3.3.5.4. Surgery

Invasive procedures are an exception in the treatment of uncomplicated TPE. They are reserved for consideration in loculated effusions that do not resolve satisfactorily after the institution of adequate treatment, or in cases of developing empyema and fibrothorax with major ventilatory interference [72]. Instillation of intrapleural fibrinolytics may have a role to play in the treatment of early TB empyema; however, surgical intervention is often required to control infection and prevent progression to fibrothorax [50].

Highlight points

Parapneumonic pleural effusion

- The diagnosis of parapneumonic pleural effusion can often be challenging and delayed with clinical awareness being the key to minimize therapeutic disadvantages. Special alert is warranted in the elderlies, who may present with a more indolent illness.
- In the infective pleural effusion, a pleural fluid pH<7.2 [or in the absence of pH, a combination of glucose concentration <40 mg/dL (2.2 mmol/L) and a lactate dehydrogenase [LDH] >1000 IU/L] are predictors of chest tube drainage.
- Initial antibiotic treatment for suspected or confirmed pleural infection should commence before results of culture tests are available and will be dictated by the likely source of infection (community or hospital-acquired disease) which can suggest the likely (prevalent) microbes.
- Antibiotic therapy is used for two to six weeks according to clinical response since the shorter courses may result in earlier clinical relapse or progression of disease.

Empyema

- Management of empyema usually involves medical and surgical measures which aim to control the infection and to evacuate the infected material as early and completely as possible.
- Surgery should be considered without delay in patients who fail to improve with antibiotics and chest tube drainage, and who have persistent infective features like fever, neutrophil leukocytosis and raised inflammatory markers.

TB Pleural effusion

- The definitive diagnosis of TB pleural effusion depends on the demonstration of Mycobacterium tuberculosis in the sputum, pleural fluid, or pleural biopsy specimens. A reasonably confident diagnosis can also be established by finding of a histological picture of typical caseating granulomas in the parietal pleura, in association with highly supportive clinical features
- An elevated concentrations of adenosine deaminase or unstimulated interferon-γ in pleural fluid can be helpful for the diagnosis of TB etiology in the appropriate context such as high TB burden communities.
- The chemotherapeutic treatment of TB pleural effusion is the same as that used for pulmonary TB. Corticosteroid can be beneficial in selected patients who present with severe systemic symptoms, after therapeutic thoracentesis. At least two weeks of anti-TB treatment is advisable before they are given.

4 Malignant Pleural Effusions

4. Malignant pleural effusion

4.1. Introduction

Malignant pleural effusion (MPE) is a common cause of exudative effusions in clinical practice. It is diagnosed by the presence of malignant cells in the pleural fluid and/or pleural tissue. It can occur in either primary or secondary pleural malignancy, of which the latter is the usual cause. The common causes of secondary pleural malignancy are lung cancer and breast cancer. Other primary sites for pleural metastasis include lymphoma, gastrointestinal and genitourinary malignancy [73].

Once the diagnosis has been made, multiple approaches to MPE management ensue, depending on clinical state and the type of malignancy. The presence of MPE indicates the advanced nature of the disease in most cases and associated with a poor prognosis [74].

4.2. Pathophysiology

The development of MPE has been attributed to a combination of mechanisms and may even implicate molecular factors [75]. Initially tumor cells metastasize to the pleura mainly through the bloodstream and invade the visceral pleura. Most lung carcinomas translocate to the ipsilateral visceral pleura via the pulmonary vessels. Thereafter, secondary dissemination to the parietal pleural occurs by tumor seedling along adhesions or by exfoliated tumor cells floating in the effusion. The pleura may also be invaded through lymphatic spread or even through direct extension of tumors infiltrating adjacent structures (i.e. lung, chest wall, mediastinum or diaphragm) [75].

4.3. Clinical presentation

The clinical presentation of MPE can vary from largely asymptomatic to acute respiratory distress as the initial presentation. It depends on the amount of fluid present, rate of fluid accumulation and the nature of underlying malignancy. Breathlessness is a common presenting symptom, although up to a quarter of those presenting may not be unduly breathless. Constitutional symptoms, such as fatigue, feeling of weakness and weight loss may predominate in some cases. Chest pain can be caused by malignant infiltration of structures in the chest wall. The pain is usually sharp and is exacerbated by movement of the pleural surfaces, as with deep inspiration, coughing, and sneezing. Local tenderness may be elicited at the site of direct tumor invasion [74, 76].

4.4. Diagnosis

MPE is diagnosed by pleural fluid cytology and pleural biopsy after initial investigation straight with chest X ray confirms the presence of fluid.

4.4.1. Imaging

Chest X ray

It may show underlying lung cancer or lung secondaries in addition to the present of pleural fluid [76].

Thoracic ultrasound

TUS can help in distinguishing malignant pleural effusions from other causes of pleural effusion. MPE is suggested by the presence of visible pleural metastases, pleural thickening greater than 1 cm, pleural nodularity, diaphragmatic thickening measuring greater than 7mm and an echogenic swirling pattern visible in the pleural fluid [77,78].

Computerized tomography

CT scan of the chest allows assessment of the entire thorax, and the presence of a tumor in the lungs may support a clinical diagnosis of pleural malignancy. Obviously, absence of parenchymal tumor does not exclude pleural malignancy [79]. Detection of thickening of the chest wall pleura or mediastinal pleura greater than 1 cm and Irregular pleural cavities and pleural nodules suggest a high probability of MPE. Approximately 50% of patients with MPE show no pleural abnormalities on CT scan [80].

Positron emission tomography-computerized tomography

Positron emission tomography – computerized tomography (PET-CT) is done to support a diagnosis of pleural malignancy in adults when there are suspicious CT findings. Although inflammation and infection can affect the PET-CT interpretation it can be used to differentiate between benign and malignant pleural disease with moderate accuracy [81].

4.4.2. Pleural fluid cytology

Thoracentesis and pleural fluid analysis are essential basic investigations for diagnosis of MPE [82,83]. The diagnostic yield of pleural fluid cytology varies depending on tumor type, tumor load, sample quality, cytological service and availability of specific ancillary tests, e.g. gene and immunohistochemistry (IHC). Pleural fluid cytology is positive in 60% of sample with an additional detection in the second (repeat) procedure. However, further repetitions have not been shown to help the diagnosis. The combined use of pleural cytology and biopsy increases the sensitivity of the diagnosis [82]. The finding of malignant cells in fluid alone is often insufficient to guide treatment, as the targeted oncological therapy requires to establish cellular type of tumor and molecular markers for genetic expressions.

4.4.3. Pleural biopsy

Histological proof used to be the gold standard for the diagnosis of MPE, but it has been replaced by good cytological services in many cases. Pleural biopsy in addition to pleural fluid cytology can increase the diagnostic sensitivity for MPE by 7–27% [83]. Image guided biopsy and thoracoscopy have largely replaced blind biopsy due to their greater sensitivity and safety profile. CT guided biopsy of pleura has a sensitivity of 87% (if a pleural lesion is identifiable by CT) compared to blind closed needle biopsy, which has a sensitivity of 47%. The diagnostic sensitivity of image-guided pleural biopsy is increased if pleural thickening >1 cm is observed. When pleural thickening is obvious, pleural biopsy via pleuroscopy or video-assisted thoracoscopic surgery allows to visualize the pleura, take biopsy of the involved area, and drain the pleural fluid. The histological characteristics of tumor in pleural tissue will guide the subsequent oncological treatment [79].

4.4.4. Pleural fluid biomarkers

Identification of pleural fluid biomarkers to distinguish malignant pleural effusions from other causes of exudative effusions could help diagnosis. Biomarkers that have been shown to be raised in malignant pleural effusions compared to benign disease include vascular endothelial growth factor (VEGF), endostatin, matrix metalloproteinases and carcinoembryonic antigen. The diagnostic accuracy and usefulness of pleural fluid markers needs to be validated by further studies [84].

4.5. Management

The management of MPE is focused on palliation of symptoms, especially relief of shortness of breath, and improving the quality of life. Treatment approach varies depending on performance status of the patient, type of tumor and expected survival. Occasionally, treatment of the underlying cancer can cause resolution of the effusion. This may be the case with types of cancer that respond well to chemotherapy, such as small cell lung cancer and lymphoma [83].

Management options include ambulatory intermittent intervention with repeated aspiration, home-based management with indwelling pleural catheters (IPCs) (also combined with pleurodesis) and traditional inpatient admission with a chest tube and talc slurry pleurodesis. In general, selection of the most appropriate treatment approach should be individualized, while also considering patient preference. Not one option is superior to another in terms of management, and if possible, the patient and family should be involved in the decision-making process [79, 83]. In this respect, scoring systems for prognosis (survival) may help to choose the treatment options (see annex, Table 7).

4.5.1. Therapeutic thoracentesis

Simple aspiration of pleural fluid can relieve shortness of breath rapidly, but fluid and symptoms will usually recur within a couple of weeks, even in a few days in some patients. Thoracentesis is a safe procedure, and the complication rates have decreased significantly with the use of TUS. Although pleural fluid is prone to reaccumulate following thoracentesis, this procedure has advantage of guiding the best strategy for further pleural fluid control (e.g. with indwelling pleural catheter or pleurodesis), by helping to identify entrapped lung [79, 85].

Thoracentesis is associated with a significant fall in intrapleural pressure resulting in chest pain especially in the presence of entrapped lungs. The presence of entrapped lung due to visceral pleural thickening or endobronchial tumor, prevents complete lung re-expansion following drainage. In these cases, pleural drainage causes excessive negative pleural pressures (<20 cmH20) leading to adverse symptoms. Pleural manometry can measure pleural pressures during pleural aspiration, and thus predict entrapped lung [79].

4.5.2. Pleurodesis

Pleurodesis induces fusion of visceral and parietal pleura with concomitant obliteration of the pleural space. It can be accomplished via a variety of chemical or mechanical means after complete drainage of the effusion that allows parietal-to-visceral pleural apposition. Intrapleural instillation of various agents such as talc, bleomycin, tetracycline, Corynebacterium parvum and doxycycline has been used to achieve pleurodesis [83,85, 86]. Complete response occurred in 64% of patients. The success rate of the pleurodesis varies with the agent used. The most common adverse effects are pain (23%) and fever (19%). These events of pain and fever are due to inflammatory response of pleura which correlates with the likelihood of successful pleurodesis [86]. It is important to give adequate pain control during chemical pleurodesis especially with use of talc sclerosant agent.

Medical talc powder is the most widely used and effective sclerosant agent for pleurodesis. Alternative agents to talc slurry in resource limited setting are Doxycycline capsule: 200mg or 300 mg and Bleomycin (antitumor agent): 30-unit or 45-unit dissolve in 20 ml of water is usually use) [87].

4.5.3. Indwelling pleural catheter

The IPC is a silicone catheter placed in the pleural cavity and is carried through a subcutaneous tunnel with a small cuff. At the other end, the IPC is discharged through a vacuum bottle with a

one-way valve that uses negative suction to monitor flow and volume. The IPC is applied in those patients with MPE that have failed pleurodesis or in those with trapped lung (unsuitable for pleurodesis) [87]. IPCs achieved control of breathlessness and quality of life comparable to talc pleurodesis and significantly shortened the length of hospital stay. IPC-related pleural infection occurred in <5% of patients and resulted in pleurodesis in some patients [85].

4.5.4. Oncological management

There is no standard treatment protocol for MPE itself. Treatment of causative tumor may have some effect on MPE. Tyrosine kinase inhibitor is used as targeted therapy for patients with MPE who have epidermal growth factor receptor mutations. Although good results in the treatment of MPE have been reported, especially with antiangiogenic therapies (e.g., Bevacizumab) and immunotherapies, the treatment of MPE is still a clinical challenge [76]. Systemic anti-cancer therapy (SACT) should be given to patients with known primary malignancy.

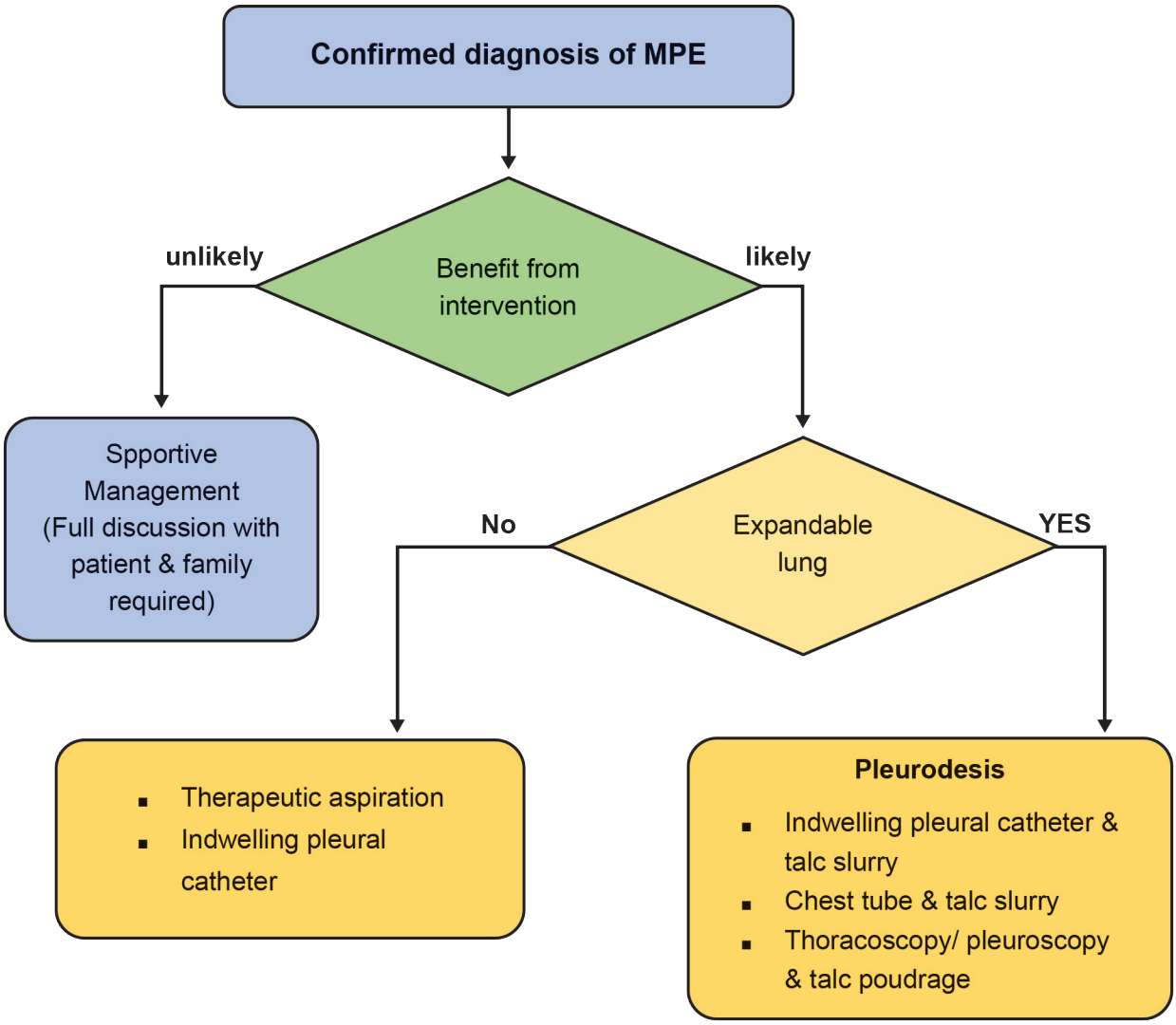


Figure 5. Management flow chart for malignant pleural effusion

4.6. Prognosis

MPE is associated with a poor prognosis [86,87]. Median survival with an MPE is 3–12 months and individualized estimates had been attempted using the LENT scoring system (pleural lactate dehydrogenase rate, neutrophil-to-lymphocyte ratio, tumor type and Eastern Cooperative Oncology Group performance status [88]. PROMISE (Prognostic and therapeutic markers of malignant pleural effusion) study was done to develop a prognostic scoring tool for 3-month mortality of patients with MPE [89]. These scoring systems may be useful to make informed decisions for choice of modality of treatment (See annex, Table 7 and 8).

Highlight points

- Diagnosis of MPE is based on the demonstration of neoplastic cells in fluid and/or pleural tissue.
- Pleural fluid cytology is positive in 60% of samples with some additional detection in the second (repeat) procedure. However, further repetitions have not been shown to help the diagnosis.
- The histological characteristic of tumor in pleural tissue is the best guide for subsequent oncological treatment.
- The management of MPE is focused on palliation of symptoms, especially relief of shortness of breath, and improving the quality of life. Treatment approach varies depending on performance status of the patient, type of tumor and expected survival.
- Management options include ambulatory intermittent intervention with repeated aspiration, chest tube drainage and pleurodesis.
- Median survival with an MPE is 3–12 months and individualized prognostic estimates have been attempted using the LENT and PROMISE scoring systems

5 Pneumothorax

5. Pneumothorax

Pneumothorax is collection of air in the pleural space, and it usually presents with dyspnea/chest pain of varying severity. Air enters the pleural space from atmosphere through the chest or from the air in larger airway via mediastinal tissue planes or direct visceral pleura perforation. Intrapleural pressure is normally negative (less than atmospheric pressure) because of opposing inward lung and outward chest wall recoil. Intrapleural pressure is increased, and lung volume is decreased by the entry of air into pleural cavity [90]. In tension pneumothorax, there is continued entry of air causing a progressive rise in intrapleural pressure and volume of air to levels that causes collapse of the lung, shift of the mediastinum to the opposite site, impaired venous return to the heart and ultimate severe hemodynamic disturbances. The degree of lung collapse determines the clinical presentation of pneumothorax [91].

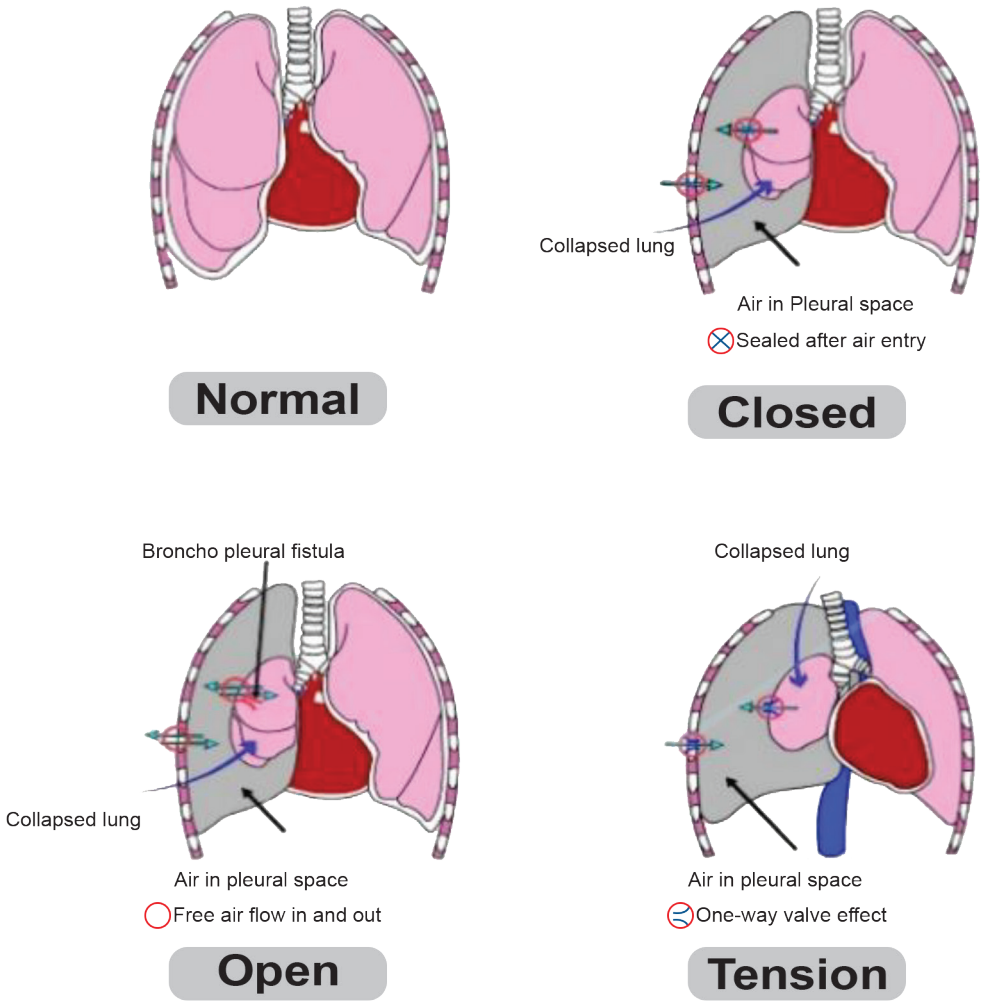
5.1. Categories

Table 4. Categories of pneumothorax

Circumstances	Pathophysiology
Traumatic (Including iatrogenic)	Simple (Closed)
	Communicating (Open)
	Tension
Spontaneous	Simple (Closed)
	Communicating (Open)
	Tension

Pneumothorax can be classified into two categories according to the circumstances in which it occurs [90,91].

1. **Traumatic pneumothorax**
    - **1.a. Traumatic** - resulted from blunt or penetrating chest trauma.
    - **1.b. Iatrogenic** - caused by inadvertent injury to pleural during medical procedures, such as the insertion of central lines, etc.
2. **Spontaneous pneumothorax** - it occurs without any apparent injury/trauma to the chest or lungs.



* Surgically 'open pneumothorax' denotes an 'open' lesion on the chest wall.

Figure 6. Illustration for pathophysiology of various types of pneumothorax

Pneumothorax can also be classified based on their subsequent pathophysiological changes into the following types [90,91]:

1. **Simple (closed)** - when the air in the pleural space does not communicate further with an outside atmosphere, and it is unlikely to cause major shift in mediastinum or hemidiaphragm.

2. **Communicating (open)** - when there is a defect in a chest wall or lung surface creating open communication with an outside atmosphere. It may produce air sucking with each breath and a paradoxical lung collapse, thus causing significant ventilatory problems.

3. **Tension** - progressive accumulation of air in the pleural cavity causing a large rise in intrapleural pressure causing the shift of mediastinum to the opposite side, resulting in compression of vena cava and other great vessels, decreased diastolic filling, and ultimately compromised cardiac output. It occurs when an injury to either chest wall or lung causes a one-way-valve situation where the air gets into the pleural cavity but is unable to escape freely and thus gets progressively trapped. Without timely treatment severe cardiopulmonary disturbance can cause systemic hypotension, respiratory arrest, and cardiac arrest within minutes.

Other terms used in clinical situations

Recurrent pneumothorax is a term used for subsequent episodes of pneumothorax occurring either on ipsilateral or contralateral site.

Catamenial pneumothorax is a rare condition that affects women of reproductive age, in a temporal relationship with menstruations. These recurrent episodes of pneumothorax occur within 72 hours before or after the start of menstruation. Although catamenial pneumothorax is often associated with the presence of thoracic endometriosis, in many cases abnormalities frequently seen at the time of surgery are diaphragmatic defects [90].

This guideline will focus on management of ***spontaneous pneumothorax.***

5.2. Spontaneous pneumothorax

Spontaneous pneumothorax develops when air enters the pleural space in the absence of any kind of trauma.

5.2.1. Types of spontaneous pneumothorax

A. **Primary spontaneous pneumothorax (PSP)** – in the absence of any known underlying pulmonary disease

B. **Secondary spontaneous pneumothorax (SSP)** – related to the presence of underlying pulmonary disease

5.2.2. Pathophysiology

The precise pathogenesis of PSP is not completely understood. With the improvement of imaging, techniques, blebs and bullae can be visualized ipsilaterally or bilaterally in CT scan in almost all patients with PSP. They are also seen during surgery and medical thoracoscopy. These changes visible on the visceral pleura have been called emphysema-like changes (ELCs) [90, 92]. It is generally assumed that pneumothorax results from the rupture of ELCs [93]. However, the exact role of blebs and bullae as a cause of air leakage in spontaneous pneumothorax is not fully understood [94].

In some patients diffuse areas of disrupted mesothelial cells are found in the visceral pleura, replaced by a layer of inflammatory cells and pores of 10–20 nm in diameter, suggesting the presence of diffuse pleural porosity. This pleural porosity is probably related to development of PSP and may explain the high recurrence (20%) of pneumothorax following bullectomy alone without an associated pleurodesis [95].

5.2.3. Clinical history and physical examination

Presenting symptoms may vary depending on the presence or absence of underlying pulmonary diseases and extent of pneumothorax. PSP is frequently observed in tall young people and often appears without inciting events. The commonest symptoms include chest pains and varying degrees of tightness and shortness of breath. Some patients may experience shoulder tip pain. In cases of SSP, breathlessness is a predominant feature. There may be history of previous pneumothorax and underlying pulmonary disease [91,92].

On examination, tachypnea, asymmetric chest expansion, reduced or absent breath sounds, hyper-resonant percussion notes and respiratory distress are suggestive signs. Hemodynamic compromise or significant hypoxia is unusual in primary pneumothorax [91].

5.2.4. Diagnosis

In view of the variability of symptoms and signs at presentation, the diagnosis of pneumothorax is usually confirmed with radiographic imaging [96].

Chest X ray

The presence of pneumothorax can be easily detected on the standard chest X ray when an appreciable amount of air is present in the pleural space [97]. The radiographic hallmark is displacement of the visceral pleural line and an absence of lung markings between the edge of the pleura and the chest wall [92].

Computerized tomography

Computed tomography scan of chest is more sensitive than chest X ray in the detection of small pneumothorax. It is not required in the majority of cases, as the diagnosis can be made on a chest X ray without difficulty. In selected cases, CT scan of chest may be needed to have more accurate assessment for management, e.g., severity and homogeneity of the bullae, suspected tube misalignment and cases requiring surgery [92].

Thoracic ultrasound

The routine use of ultrasound in PSP has not yet been well evaluated. However, TUS is a sensitive technique in the diagnosis of pneumothorax in trauma and critically ill patients [98].

5.2.5. Management of primary spontaneous pneumothorax

Management of PSP has two goals: evacuation of air, if needed, and the prevention of recurrence. The treatment of pneumothorax may vary from conservative management to immediate needle decompression or insertion of intercostal tube to drain the air. Patient's choice should be considered in all cases except in cases with severe hemodynamic deterioration. All treatment options should be discussed with the patient to determine the best option, with consideration for the least invasive treatment [90,91.92].

For management it is necessary to know whether it is

1. the first episode of pneumothorax

   or

2. persistent or recurrent pneumothorax

5.2.5.1. Management of first episodes of pneumothorax

Treatment options vary widely from observation, supplemental oxygen, needle aspiration of intrapleural air, chest tube insertion (i.e. tube thoracostomy) to even surgery (VATS or open thoracotomy). The choice of treatment depends on patient characteristics and clinical circumstances [96].

Conservative management

Conservative management is often undertaken in patients with small or incidental PSP but could be an alternative to needle aspiration or chest drain in patients with bigger pneumothorax [99]. Patients who are clinically stable and having their first episode of PSP can be observed with supplemental

oxygen if they are not breathless and their pneumothorax is small (2–3 cm between the lung and chest wall on a chest X ray) [100]. Conservative management of PSP is as effective as interventional management in selected patients, with a low risk of serious adverse events [101.] The patient is observed and reviewed as frequently as necessary to know whether intervention is required or not in time.

Percutaneous Needle aspiration

Needle aspiration is appropriate for patients with a first episode of PSP having no evidence of underlying lung disease. However, they should have either shortness of breath or a pneumothorax with a rim of air measuring at least 2 cm when assessed at the level of the hilum [102]. Needle aspiration is well tolerated, is associated with fewer adverse events and has a shorter duration of hospitalization. But unsurprisingly it is associated with a higher failure rate compared to chest tube drainage where continuous evacuation is guaranteed [103]. This option is better reserved for an urgent situation where other alternative treatments are not available at the time of diagnosis.

Intercostal drainage

Unstable clinical state, bilateral pneumothorax, hemopneumothorax and recurrent PSP are conditions where chest tube insertion should be considered. Most patients with PSP can be managed successfully with a small chest tube (≤22 Fr) or chest catheter (≤14 Fr) [96].

The chest tube can be connected to a water sealed device, with or without suction and left in position until the pneumothorax resolves. If the pneumothorax fails to resolve with a chest tube, suction if not already on, can be applied. Suction is thought to remove air from the pleural cavity at a rate that exceeds the egress of air through the breach in the visceral pleura and subsequently promote healing by apposition of the visceral and parietal pleural layers [96].

Chest tube drainage shows a higher “immediate success” rate compared to needle aspiration whereas success rate (calculated at day 7 or later) appears similar between chest tube drainage and needle aspiration [104]. There may be tissue injury, pain, bleeding, infection and an increased risk of subcutaneous emphysema following chest tube drainage. Surgical emphysema can also occur with an imbalance between a large air leak and a relatively small-bore chest drain. It usually subsides spontaneously after a few days, but it may occasionally lead to acute airway obstruction if it involves mediastinum or thoracic compression [96, 104].

Ambulatory management

This model of management is used in some centers for patients undergoing conservative treatment or with a special minimally invasive device. Ambulatory treatment using a purpose made device containing a one-way valve, or Heimlich valve attached to chest drain has the potential to allow outpatient management of pneumothorax. Ambulatory management can be considered for the initial treatment of primary spontaneous pneumothorax in adults with good support and in centers with available expertise and follow-up facilities. A reduction in the length of hospital stay was observed in centers where ambulatory management was offered [14,96].

5.2.6. Persistent air leak

Patients who show air leak longer than 5-7 days could be presumed to have persistent air leak. It can be caused by either an alveolar-pleural fistula (APF) or bronchopleural fistula (BPF). Post-operative persistent air leak is not uncommon. They may also occur after spontaneous pneumothorax with underlying lung disease. Chest X ray shows failure of the lung to re-expand. CT chest is useful to detect the cause and evaluate for further management [105].

5.2.6.1. Management of Persistent air leak

Spontaneous closure can occur with chest tube drainage. Patients being treated with chest tube show signs suggestive of PAL beyond 4 days should be evaluated for surgery to close the air leak followed by pleurodesis to prevent recurrence [106].

For PALs in patients who have recently undergone thoracic surgery or in whom surgery would be contraindicated based on the severity of illness, there are other treatment options such as chemical pleurodesis, autologous blood patch pleurodesis, and most recently, endoscopically placed “one-way” valves to temporarily “plug” the airway [106].

5.2.7. Surgical management

Surgical treatment is considered in management of a persistent air leak or prevention of recurrence in patients whose initial pneumothorax has resolved. It may be considered for the treatment of pneumothorax in adults at initial presentation if recurrence prevention is deemed important (e.g. patients presenting with tension pneumothorax, or those in high- risk occupations). Blebectomy of visible blebs is an option for them. [96]

Surgical approach can be either via thoracotomy or via video-assisted thoracoscopic surgery (VATS) whereby instruments are introduced into the pleural cavity via ports in the chest wall. Thoracotomy access and surgical pleurodesis should be considered to achieve the lowest level of recurrence risk required for specific (e.g. high risk) occupations. VATS access can be considered for surgical pleurodesis in the general management of pneumothorax in adults [90].

The rate of pneumothorax recurrence after surgical intervention appears to be very low. However, pneumothorax recurrence rate and the need for further procedures appear to be slightly higher following VATS when compared with thoracotomy. On the other hand, length of hospital stays, post-operative pain and complications appear to be reduced following VATS when compared with thoracotomy [14, 92].

5.2.8. Surgical referral

Help of surgical colleagues should be considered in the following circumstances [14]:

- First pneumothorax presentation associated with tension and first secondary pneumothorax associated with significant physiological compromise
- Second ipsilateral pneumothorax
- First contralateral pneumothorax
- Synchronous bilateral spontaneous pneumothorax
- Spontaneous hemopneumothorax
- Persistent air leak or failure of lung re-expansion
- Professions at risk of recurrence (e.g. pilots and divers)
- Pregnancy

5.3. Recurrent pneumothorax

Recurrence following SP is a frequent concern and overall occurs in up to 32% of patients after a single episode of PSP and 13-39% after a first episode of SSP [14]. Low BMI is an established risk factor for the initial development of PSP and may be associated with increased risk of recurrence of SP. This increased risk of SP in low BMI is probably due to nutritional deficiencies affecting α1-antitrypsin levels or due to unbalanced physical development [92]. An increased rate of recurrence was observed in female patients in the age group 31–50 years. Some of them had specific pathophysiology,

including lymphangioleiomyomatosis and catamenial pneumothorax [107]. Smoking cessation was found to be linked with reduced risk of PSP recurrence. Recurrence rates are higher in patients who have blebs or bullae on high-resolution CT scan [107].

5.3.1. Management of recurrent pneumothorax

Surgery is an effective treatment for recurrent pneumothorax. It can be done either electively or at the episode of pneumothorax to reduce recurrence. The main procedures are surgical pleurodesis (pleurectomy, mechanical abrasion) and bullectomy of visible blebs either via thoracotomy or VATS. Currently, it is considered for patients who have had more than one recurrence [92].

Another non-operative method is medical (chemical) pleurodesis. Pleurodesis aims to achieve obliteration of the pleural space. It can be performed by instilling a chemical irritant. Currently, talc is the most common agent used for pleurodesis. It is administered as poudrage by thoracoscopy (VATS or pleuroscopy) or as slurry via a chest tube [108,110]. Pain is the main postoperative adverse symptom after talc pleurodesis and should be adequately controlled as in the management of MPE.

5.4. Discharge advice, flying and activity

All patients discharged after treatment should be given verbal and written advice to return to the Emergency department immediately if they develop recurrent or further breathlessness. It is recommended that all patients should be follow-up to ensure resolution of the pneumothorax, and for subsequent management as required. Emphasis should be placed on smoking cessation as an affective preventive measure to reduce recurrences [14, 92, 104].

Patients with persistent closed pneumothorax (i.e. incompletely resolved on chest X ray) should not travel on commercial flights until complete radiological resolution. They should wait for at least 7 days after complete resolution. After having pneumothorax, sports and jobs involving pressurized environment (e.g., diving) should be discouraged permanently unless an effective preventive treatment had been taken [14].

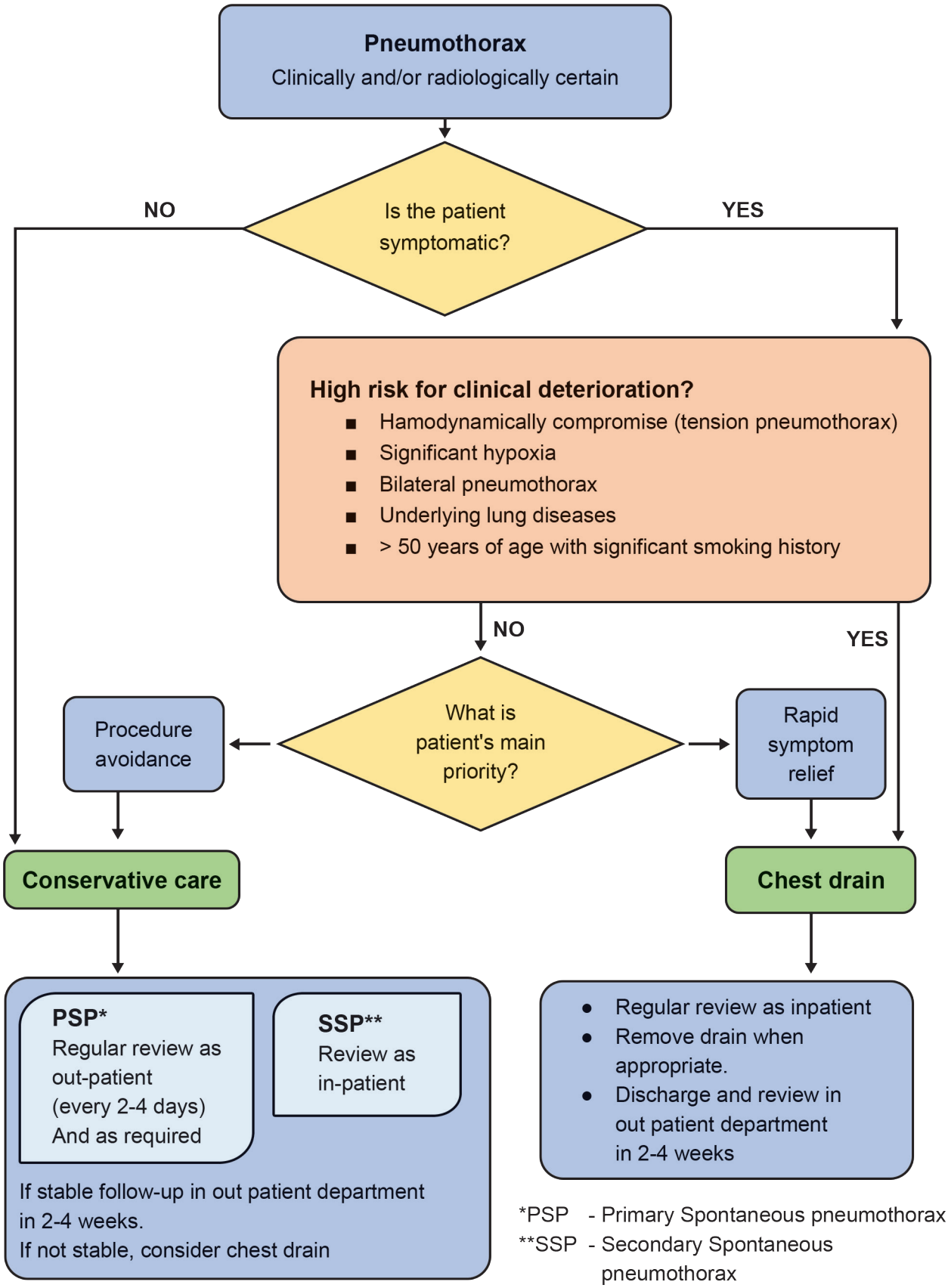


Figure 7. Management flow chart for spontaneous pneumothorax

Highlight points

- Diagnosis of pneumothorax commences with clinical detection and is confirmed with radiographic imaging. The radiographic hallmark is displacement of the visceral pleural line and an absence of lung markings between the edge of the pleura and chest wall.
- Management of primary spontaneous pneumothorax has two goals: evacuation of air, if needed, and the prevention of recurrence.
- Treatment options include observation, supplemental oxygen, needle aspiration, chest tube insertion (i.e. tube thoracostomy) and surgery (VATS or open thoracotomy).
- A persistent air leak is presumed when an air leak persists for greater than 5–7 days and can be caused by either an alveolar-pleural fistula (APF) or bronchopleural fistula (BPF).
- Recurrence following SP occurs in up to 32% of patients after PSP and 13-39% of SSP.
- Management of recurrent pneumothorax includes surgical pleurodesis or bullectomy of visible blebs either via thoracotomy or VATS. Medical pleurodesis is an alternative option for patients who are not fit or unwilling for invasive procedures.

6 Miscellaneous

6. Miscellaneous

Mangement of chylothorax, malignant pleural mesothelioma and some common pleural effusions associated with non-plumonary diseases are described in this section.

6.1. Chylothorax

A chylothorax is caused by the extravasation of chyle into the pleural space due to obstruction or injury to the thoracic duct or its tributaries or transdiaphragmatic flow from the peritoneal cavity. The pleural fluid is often milky in appearance and is characterized by elevated triglycerides and the presence of chylomicrons [110].

It is also known as chylous pleural effusion, is an uncommon cause of pleural effusion with a wide differential diagnosis. As the normal chyle production is around 2.4 liters per day, a considerable amount of chyle can accumulate in the pleural cavity in a very short period. Chylothorax can lead to significant morbidity and mortality [109].

6.1.1. Etiology

There are three main types of etiologies in chylothorax:

- traumatic,
- non-traumatic, and
- idiopathic.

The most common form of chylothorax is non-traumatic and a common cause is malignancy. Other causes of non-traumatic chylothorax include congenital (e.g.- lymphangiectasis), infective (eg. Tuberculosis) and rare causes (e.g. angiofollicular lymph node hyperplasia known as Cattleman's disease, sarcoidosis) [109, 110].

Traumatic chylothorax is further subclassified as iatrogenic (surgical) or non-iatrogenic (penetrating or blunt trauma to chest). Idiopathic causes account for nearly 10% of all cases of chylothorax [111,112]. Chylothorax is considered to be idiopathic after extensive investigation does not reveal any plausible cause for it. [109, 110]

Chylous effusion is odorless, and the high triglyceride content and chylomicrons give it a milky appearance. A somewhat similar appearance can be seen in pseudo-chylothorax. Pseudo-chylothorax (also known as chyliform effusion) results from long-standing pleural effusion that mimics the

appearance of chylothorax but lacks the chylomicrons that confirm a definitive diagnosis of chylothorax [109].

6.1.2. Clinical presentation

The clinical features of chylothorax depend upon the causes and rapidity of accumulation. Small chylothorax can be asymptomatic and is detected incidentally. Patients with large chylothorax usually present with symptoms and signs caused by the mechanical effect of compression on the lung. The main symptom of chylothorax is shortness of breath. Some people also experience chest tightness, tiredness (fatigue) and weight loss. Fever and chest pain are usually absent. Post-traumatic chylothorax can present up to 10 days after the inciting trauma [113].

Physical signs of pleural effusion are elicited usually on one side. Due to the location of the thoracic duct, the right side is more common than the left, accounting for two-thirds of the total cases [113].

6.1.3. Diagnosis

6.1.3.1. Imaging

The usual imaging techniques (Chest X ray, TUS) cannot suggest the nature of the pleural fluid.

CT scan chest

CT scan is possibly more useful for the diagnosis of chylothorax. It can show cisterna chyli in around 2% of cases. Due to the high amount of fat content, it is seen as a low-attenuation tubular area in the posterior mediastinum. It may suggest the cause of chylothorax e.g. mass or obstructive lesion in the posterior mediastinum, or evidence of trauma [109, 113].

6.1.3.2. Lymphangiography or lymphoscintigraphy

They are special imaging tests used to delineate the lymphatic system. This can show any leakage in the thoracic duct leading to chylothorax. However, their use is uncommon due to its invasive nature and limited relevance to management [113].

6.1.3.3. Pleural fluid analysis

Based on the amount of fat content in chylothorax, the appearance of fluid can be (white) milky, opalescent and rarely looks like serous, or serosanguineous. In chylothorax, after the centrifugation

of the pleural fluid, the supernatant is opaque, in contrast to clear appearance in empyema. Chylothorax is usually alkaline, with PH ranging from 7.4 to 7.8 [109].

The pleural fluid triglyceride concentration greater than 110 mg/dL confirms the diagnosis of chylothorax. If a pleural effusion contains triglycerides between 50 and 110 mg/dL, analysis of the lipoprotein content of the pleural fluid may be useful [112,113]. Detection of chylomicrons in the pleural fluid by lipoprotein electrophoresis confirms chylothorax. Typically, the total cholesterol level in a chylothorax is less than 200 mg/dl [109].

In pseudo-chylothorax or chyliform effusion, gross appearance may mimic the chylothorax and it is caused by long-standing exudative pleural effusion of various causes (commonly tuberculosis and chronic rheumatoid arthritis). The cholesterol concentration in pseudo-chylothorax is typically more than 200 mg; triglycerides level is less than 110 mg/dL, and cholesterol to triglycerides ratio is always more than 1. The presence of cholesterol crystals is virtually diagnostic of pseudo-chylothorax [109, 113].

Table 5. Pleural fluid values in chylorhorax and pseudochylothorax [110]

Pleural fluid parameter	Chylothorax	Pseudochylothorax (chyliform effusion)
1. Triglyceride	High (>110 mg/dl)	Low (<110mg/dl)
2. Cholesterol	Low	High (>200mg/dl)
3. Cholesterol crystal	Absent	Often present
4. Chylomicrons	Usually present	Absent

6.1.4. Management

After drainage of the fluid from the pleural space, subsequent management of chylothorax varies from conservative measures to surgical treatment and, more recently, interventional radiological techniques. Appropriate nutrition, electrolyte replacement, and fluid replacement are the cornerstones of treatment [110, 113].

Surgery is particularly considered if the case is post-traumatic or iatrogenic refractory to other treatments. Surgical interventions include ligation of thoracic duct, pleuroperitoneal shunting and pleurodesis [112, 113].

6.2. Malignant pleural mesothelioma

Malignant mesothelioma is a tumor arising from the mesothelial lining of the pleura, peritoneum, pericardium and tunica vaginalis. Malignant pleural mesothelioma (MPM) is the most common among them, accounting for approximately 90% of malignant mesothelioma. Most patients of mesothelioma are older adults who have worked in environments containing asbestos which is a banned substance nowadays [114]. The risk is greater with longer exposure. MPM represents a significant diagnostic and therapeutic challenge and is associated with poor prognosis [115].

6.2.1. Categories

Mesothelioma is classified into three categories based on the types of cells [116].

- Epithelioid mesothelioma: The most common form of malignant mesothelioma (60% to 80% of cases)
- Sarcomatoid mesothelioma: The rarest form of malignant mesothelioma (10% of cases). It grows faster and is harder to treat than epithelioid mesothelioma
- Biphasic mesothelioma: A form of malignant mesothelioma (10% to 15%) containing a mix of epithelioid and sarcomatoid cell types

6.2.2. Clinical Presentation

The clinical manifestations of MPM are usually nonspecific and insidious [117]. The tumor may appear 20 to 50 years (or more) after exposure to asbestos. They present with symptoms of pleural effusion such as shortness of breath, chest pain and cough. Among them chest pain is the notable symptom. Tumor invasion of chest wall may cause bone pain and neuropathic pain appears when tumor invades intercostal, paravertebral or brachial nerve plexuses. It can also present with pneumothorax. Compared to lung cancer, distant metastases are usually rare probably because of short survival time [116].

6.2.3. Diagnosis

The diagnosis of MPM may be suspected based on chest X-ray and CT scan findings, and is confirmed by either examining pleural fluid or by a tissue biopsy of the tumor [115].

Chest X ray usually shows a unilateral pleural effusion and/or pleural thickening. Chest CT scans with intravenous contrast agent (optimized for pleural evaluation) is the modality of choice for initial evaluation of patients with suspected MPM. Chest CT scan showing diffuse or nodular pleural thickening, especially involving mediastinal pleura is suggestive of MPM.[115, 116].

Blind closed pleural biopsy has a low sensitivity for detection of mesothelioma. Image-guided pleural biopsy gives additional positive yield. Transthoracic biopsy can be associated with tumor deposition along the needle tract. Thoracoscopic biopsies (performed by VATS or pleuroscope under local or general anesthesia) are the standard investigative procedure for a pleural effusion where mesothelioma is highly possible. As well as securing a pathological diagnosis, it also allows evacuation of symptomatic pleural effusion and pleurodesis using talc poudrage. In addition, it permits the assessment of the pleural cavity for staging purposes of MPM [115.117].

Biomarkers have been studied for the diagnosis and prognosis of MPM with varying specificity and sensitivity. Among these, pleural fluid mesothelin has been widely tested and was not found to have significant sensitivity and specificity for the diagnosis of malignant mesothelioma [14].

6.2.4. Management

MPM is generally not responsive to radiation and chemotherapeutic treatment. Long-term survival and cures are exceedingly rare [117]. Pleurodesis may be performed to prevent recurrent fluid accumulation. Chemotherapy often use cisplatin and pemetrexed with the addition of bevacizumab. The combination regimens (using immune checkpoint inhibitors, combined immune checkpoint inhibitors plus chemotherapy, or combinations of other agents) are being investigated [119]. The percentage of people that survive five years following diagnosis is on average 8% in the United States. Good-quality palliative care is vital for MPM patients [120].

6.3. Some common pleural effusions associated with non-pulmonary diseases

This section will focus on three frequently encountered pleural effusions; those accompanying cardiac failure, hepatic disfunction and renal insufficiency.

6.3.1. Cardiac failure

Pleural effusion associated with cardiac decompensation is not uncommon in clinical practice. It is perhaps the most common cause of transudative effusion. Cardiac failure leads to excess pleural effusion formation by way of an increase in pulmonary capillary pressure and a consequent leak into the pleural space. This rise of pressure can happen in a range of cardiac diseases including left ventricular dysfunction, which may be diastolic or systolic, valve dysfunction or constrictive pericarditis [121]. Elevated systemic pressure leads to effusion formation by increasing filtration across the systemic circulation of the parietal pleura and by decreasing lymphatic flow through an increase in the downstream venous pressure. Similarly, an elevated pulmonary pressure could result in pleural effusion formation by increasing filtration across the pulmonary circulation of the visceral pleura [122].

These effusions are frequently small in volume, usually occupying one third or less of the hemithorax. Occasionally, fluid may collect within the interlobular fissures, simulating a mass that disappears with diuretic therapy (vanishing tumor). They are bilateral in many cases [121].

Diagnosis is made by the presence of clinical signs confirmed by chest X ray. Thoracentesis may be required when pleural effusion fails to respond to diuresis, or when the patient has pleuritic pain or fever suggesting an additional process, such as pneumonia, pulmonary embolism [121].

Pleural fluid is usually transudative in nature. N-terminal pro-brain natriuretic peptide (NT-proBNP), a peptide produced by cardiomyocytes in response to parietal stress in heart failure, has been found to be highly sensitive and specific (94%) in differentiating cardiac from non-cardiac effusions. A NT-proBNP >1500 pg·mL−1 gives a confirmation for heart failure [123]. But it is rarely measured in pleural fluid as it is also raised in blood which is easily measured.

Majority of pleural effusion caused by cardiac failure will improve with adequate medical management [124]. Presence of refractory pleural effusion in patients with decompensated CHF has a 1-year mortality of 50% despite adequate medical treatments.

Refractory effusion may be treated by thoracentesis and drainage of fluid, primarily for palliative purposes. Repeat thoracentesis may be required frequently to get relief from dyspnea and/or chest discomfort. In such cases, IPC and pleurodesis may be considered [123].

6.3.2. Hepatic hydrothorax

Hepatic hydrothorax occurs in cirrhotic patients with portal hypertension without an underlying cardiac or pulmonary disease [125]. Unilateral effusion is commoner than bilateral occurrence. Whilst often associated with ascites, up to 10% will not have either clinically or radiologically detectable ascites [126].

More than one mechanism may be involved in pleural fluid accumulation including azygous vein hypertension, hypoalbuminemia and transdiaphragmatic fenestrations [127]. Although many patients remain asymptomatic with large volumes of ascites, respiratory symptoms will usually result from a comparatively smaller amount of fluid accumulation in the pleural cavity. HH can present with varying severity, pleuritic chest pain and nonproductive cough [126].

HH should be suspected in patients with, (or without), known cirrhosis and ascites developing unilateral (especially right sided) transudative effusions in the absence of underlying cardiac, pulmonary, or renal pathology. Analysis of pleural aspiration confirms a transudative nature of effusion [128].

The mainstay of treatment is diuretic therapy, dietary salt restriction to 2 g per day, and management of the underlying hepatic condition [129]. Other measures include alcohol abstinence, avoidance of medications which decrease systemic blood pressure and/or impaired renal perfusion (angiotensin-converting enzyme-inhibitors and nonsteroidal anti-inflammatory drugs) [124].

Despite adequate medical therapy, 21–26% of patients suffer from refractory hepatic hydrothorax and will require additional palliative and therapeutic options. Repeated thoracentesis is a generally accepted strategy and can relief dyspnea in patients with HH. The intercostal tube insertion for the management of symptomatic refractory hepatic hydrothorax is shown to carry a high morbidity and mortality. Tube drainage can be associated with development of pneumothorax, empyema, and electrolyte imbalance and renal dysfunction [123]. Thoracoscopy and chemical pleurodesis with talc powder are also unfavorable treatment options and are considered in selected patients with HH. However, video-assisted thoracoscopy may be done to repair diaphragmatic defects (with or without talc pleurodesis) with full awareness of some possible complications (fever, renal failure, pneumothorax, pneumonia, liver failure, pleural infection). Indwelling pleural catheters (IPCs) are being considered as a potential option for HH. Placement of IPCs is associated with spontaneous

pleurodesis in about one third of patients. IPCs can be used as a mode of palliation, after careful assessment of risks, benefits, and alternatives and if possible, should be avoided in transplant candidates [129].

Transjugular intrahepatic portosystemic shunts (TIPS) may be useful in selected patients. Development of HH is a recognized indication for liver transplant [129].

6.3.3. Renal insufficiency

Pleural effusions are seen in 20% of patients on regular hemodialysis. They are a marker of severe disease and are usually due to fluid imbalances [130]. Cardiovascular disease is common in patients with end-stage renal disease (ESRD) and other potential mechanisms of fluid overload are pulmonary over-hydration secondary to water and solute retention, hypoproteinaemia, high-output arteriovenous fistula, or injury of the alveolo-capillary membrane secondary to toxic-lesional factors. Effusions associated with renal failure are frequently bilateral (70%) [131]. Pleural effusion could be transudative as well as exudative depending on the underlying causes. In renal failure effusion can be due to uremia itself or other causes such as cardiac failure, parapneumonic effusion and TB pleural effusion [132, 133]. Peritoneal dialysis can also be complicated with occurrence of pleural effusion [134].

Most patients respond to volume balance and optimization by hemodialysis and diuretics or a combination of these modalities. Thoracentesis is considered only when dyspnea does not respond to these measures in bilateral transudative effusion. Early thoracentesis should be done in the patient with a unilateral pleural effusion to detect underlying causes like parapneumonic effusion and TPE. They are treated accordingly if the etiological causes other than renal insufficiency are identified [133].

Highlight points

- In Chylothorax, the pleural fluid triglyceride concentration is > 110 mg/dL and total cholesterol level is < 200 mg/dl whereas the cholesterol concentration in is typically > 200 mg and triglycerides level is < 110 mg/dL in pseudo-chylothorax.
- Malignant pleural mesothelioma may be suspected based on chest X-ray and CT scan findings and is confirmed by either examining pleural fluid or by a tissue biopsy of the tumor.
- Serum NT-proBNP should be considered to support diagnosis of heart failure with pleural effusion in differentiating cardiac from non-cardiac causes.
- Hepatic hydrothorax can occur in patients with cirrhosis and portal hypertension. The presence of cirrhosis is not previously known in some cases.
- Pleural effusion in the renal failure is usually due to fluid imbalance. But it can be due to uremia itself or other causes such as cardiac failure, parapneumonic effusion, TB pleural effusion and peritoneal dialysis.

7 Conclusions and Future Directions

7. Conclusions and future directions

The clinical practice guidelines have been developed with references on international guidelines, contextual information and contribution by national experts. Pleural diseases represent a diagnostic challenge, with heterogenous clinical presentations and causes. This guideline provides updated strategies to diagnose different pleural diseases. It includes the current management for clinically important pleural diseases. As for all guidelines periodical revisions and updates will follow as evidence-based information accumulates with times.

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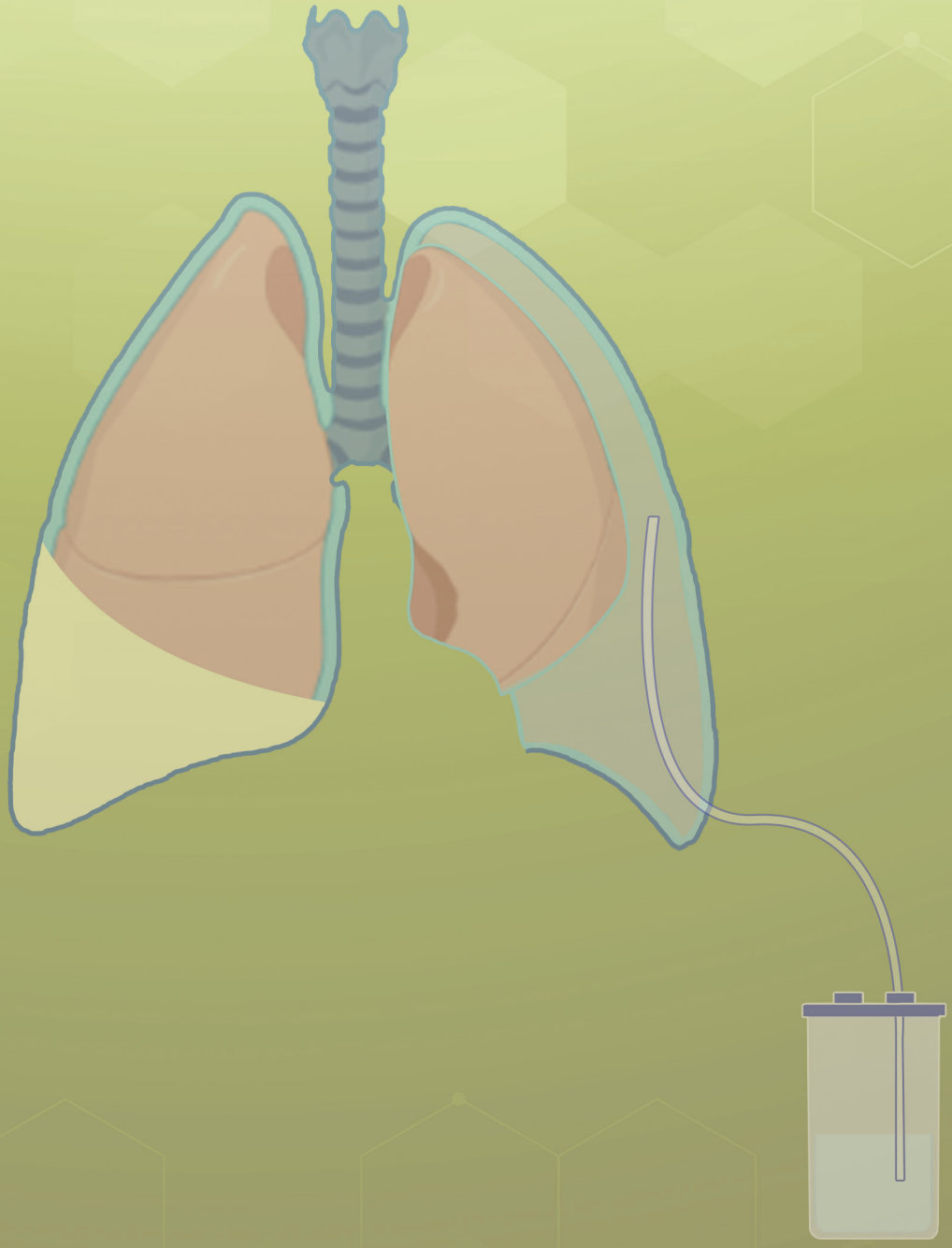
9 Annexes



9. Annexes

Table 6. Parameters of the RAPID Score

Parameter	Measure		Score
Renal	Urea	<5 mmol/L 5-8 mmol/L >8 mmol/L	0 1 2
Age	Age	<50 years 50-70 years >70 years	0 1 2
Purulence of fluid	Purulent Non-purulent		0 1
Infection source	Community-acquired Hospital-acquired		0 1
Dietary factor	Albumin	>27 mmol/L <27 mmol/L	0 1
			Total Scores
Risk categories	**Low risk** **Medium risk** **High Risk**		**Score 0-2** **Score 2-4** **Score 5-7**

Table 7. The LENT score calculation

Variables			Score
L-LDH level in pleural fluid (IU/L)	<1,500 >1,500		0 1
E-ECOG PS *	0 1 2 3-4		0 1 2 3
N-NLR **	<9 >9		0 1
T-Tumor type	Lowest risk tumor types Moderate risk tumor type Highest risk tumor types	Mesothelioma, hematological malignancy Breast cancer, gynecological cancer Renal cell carcinoma, lung cancer, other tumor types	0 1 2
			Total Scores
Risk categories	**Low risk** **Moderate risk** **High risk**		**0-1** **2-4** **5-7**

***ECOG PS**: Eastern Cooperative Oncology Group Performance Score

****NLR**: Neutrophil to lymphocyte ratio

Table 8. The clinical PROMISE score and risk category

Variable		Score
Chemotherapy	No Yes	0 4
Radiotherapy	No Yes	0 2
Hemoglobin (g/dL)	>16 14-16 12-14 10-12 <10	0 1 2 3 4
WBC (109 cells/L)	<4 4-6.3 6.4-10 10-15.8 >15.8	0 2 4 7 10
CRP (IU/L)	<3 3-10 10-32 32-100 >100	0 3 5 8 10
ECOG performance status	0-1 2-4	0 7
Cancer type	Mesothelioma Other cancer type Lung cancer	0 4 5
		Total Score
Risk category	**Category A: (<25%)** **Category B: (25-50%)** **Category C: (50-75%)** **Category D: (>75%)**	**Score 0-20** **Score 21-27** **Score 28-35** **Score >35**

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